ORGANIC LETTERS

2000
Vol. 2, No. 10
1345−1348

β-Scission of the N–O Bond in Alkyl Hydroxamate Radicals: A Fast Radical Trap

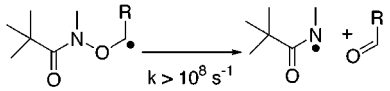
Min Wu and Tadhg P. Begley*

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853

tpb2@cornell.edu

Received December 22, 1999

ABSTRACT

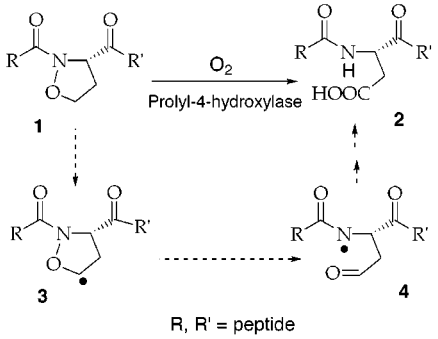


R = methyl, cyclopropyl or 2-phenylcyclopropyl

The rate of the β-scission of the N–O bond in the alkyl hydroxamate radical is faster than 2×10^8 s^{-1}. This reaction may be useful as a radical trap.

During our studies on the mechanism of inactivation of prolyl-4-hydroxylase by 5-oxaproline-containing peptides, we identified **2** as the product of the enzyme catalyzed oxidation of **1**.[1] This suggested that N−O bond cleavage from the putative radical intermediate **3** had occurred (Scheme 1).

Scheme 1



While N−O bond fragmentation reactions β to a radical center have been previously described,[2] we tested the plausibility of our proposal on a structure more closely related to **3**. In this communication, we describe a small molecule model system **12** (Scheme 2) in which we have been able to duplicate the N−O bond fragmentation and estimate a lower limit for the rate of this reaction.

The synthesis of the model system **12** is outlined in Scheme 2. Irradiation of **12** with a tungsten lamp in the presence of *tert*-butyl thiol resulted in the formation of amide **19** which was isolated in 82% yield and the disulfide **15**. We suggest that these products were formed from radical **14**. Decarboxylation of **14** would give radical **16**, the analogue of the putative enzyme-generated radical **3**. Cleavage of the NO bond of **16** would give **17** which would then abstract a hydrogen atom from *tert*-butyl thiol to give amide **19**.

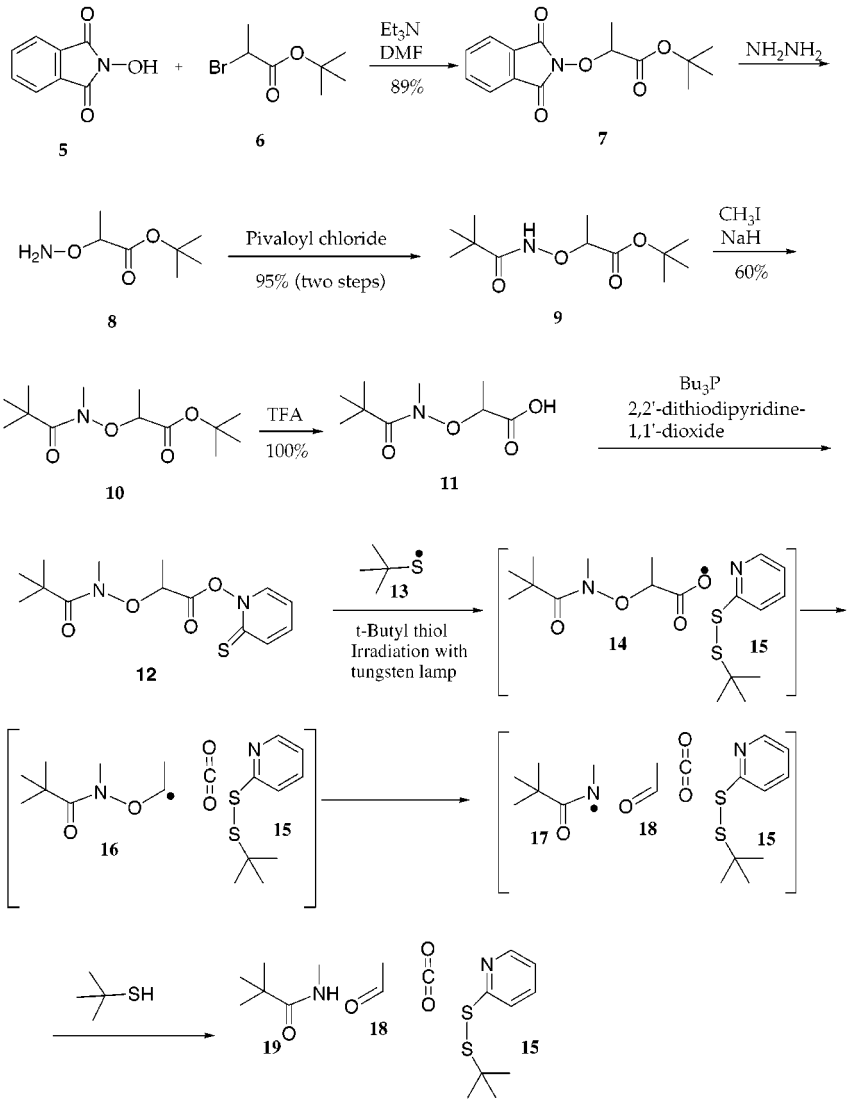
To estimate the rate of the N−O bond cleavage, the methyl group of **12** was replaced with a cyclopropyl group. For this compound (**20**), we expected that ring opening of

(1) Wu, M.; Moon, H.-S.; Begley, T. P.; Myllyharju, J.; Kivirikko, K. I. *J. Am. Chem. Soc.* **1999**, *121*, 587.

(2) (a) Crich, D.; Huang, X.; Newcomb, M. *Org. Lett.* **1999**, *1*, 225. (b) Martin, A.; Rodriguez, M.; Suarez, E. *Tetrahedron Lett.* **1999**, *40*, 7525. (c) Clark, A. J.; Peacock, J. L. *Tetrahedron Lett.* **1998**, *39*, 6029. (d) Boivin, J.; Fouquet, E.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1769. (e) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 4299.

10.1021/ol991392l CCC: $19.00
Published on Web 04/26/2000

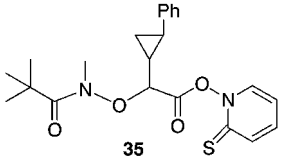
Scheme 2



the cyclopropyl group of **21** would compete with the N−O bond fragmentation and that the ratio of **19** to **25** would allow us to estimate the N−O bond fragmentation rate (Scheme 3).

The synthesis of **20** is outlined in Scheme 4. Compound **20** was photolyzed in CD_2Cl_2 under the same conditions used for the photolysis of **12**. Analysis of the photolysis mixture by NMR and by GC/MS demonstrated the formation of aldehyde **23** and amide **19**. The product **25** resulting from opening of the cyclopropyl ring of **21** was not detected (detection limit < 10%). The product **22** resulting from direct hydrogen atom abstraction by **21** was also not detected. The ring-opening rate of the trimethylsiloxycyclopropylmethyl radical is $2 \times 10^7 s^{-1}$.[3] If we assume that this is a reasonable approximate model for the rate of the cyclopropyl ring opening in **21**, we can estimate the rate of the N−O bond cleavage in **21** to be greater than 2×10^8 s^{-1}.

The methyl group of **12** has also been replaced with a phenyl-substituted cyclopropyl group (**35**). Photolysis of this compound resulted in a more complex reaction mixture than



(3) (a) Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537. (b) Nonhebel, D. C.; Suckling, C. J.; Walton, J. C. *Tetrahedron Lett.* **1982**, *23*, 4477.

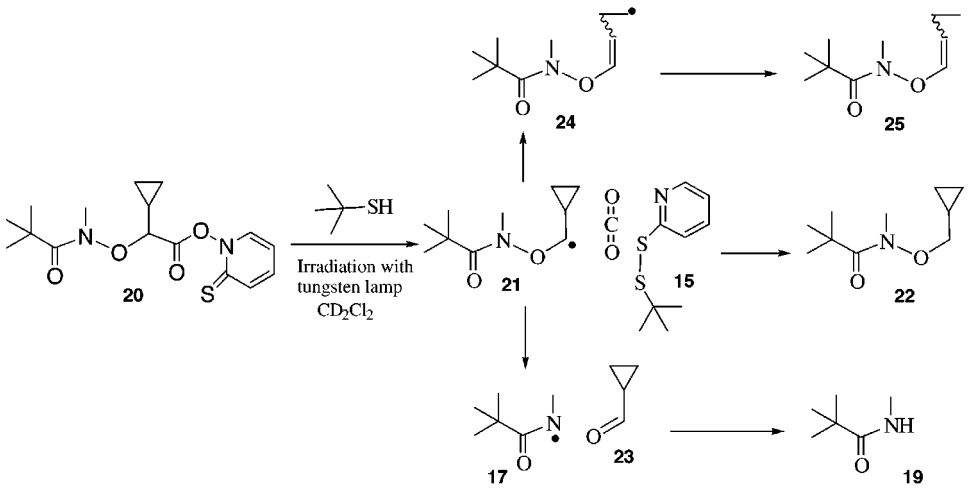
(4) Newcomb, M.; Choi, S.-Y.; Toy, P. H. *Can. J. Chem.* **1999**, *77*, 1123.

(5) (a) Franot, C.; Mabic, S.; Castagnoli, N., Jr. *Bioorg. Med. Chem.* **1998**, *6*, 283. (b) Franot, C.; Mabic, S.; Castagnoli, N., Jr. *Bioorg. Med. Chem.* **1997**, *5*, 1519. (c) Kim, J -M.; Hoegy, S. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1995**, *117*, 100. (d) Silverman, R. B. *Acc. Chem. Res.* **1995**, *28*, 335. (e) Silverman, R. B.; Lu, X. *J. Am. Chem. Soc.* **1994**, *116*, 4129.

(6) Baldwin, J. E.; Adlington, R. M.; Domayme-Hayman, B. P.; Knight, G.; Ting, H.-H. *J. Chem. Soc., Chem. Commun.* **1987**, *21*, 1661.

(7) Baldwin, J. E.; Adlington, R. M.; Crouch, N. P.; Keeping, J. W.; Leppard, S. W.; Pitlik, J.; Schofield, C. J.; Sobey, W. J.; Wood, M. E. *J. Chem. Soc., Chem. Commun.* **1991**, 768.

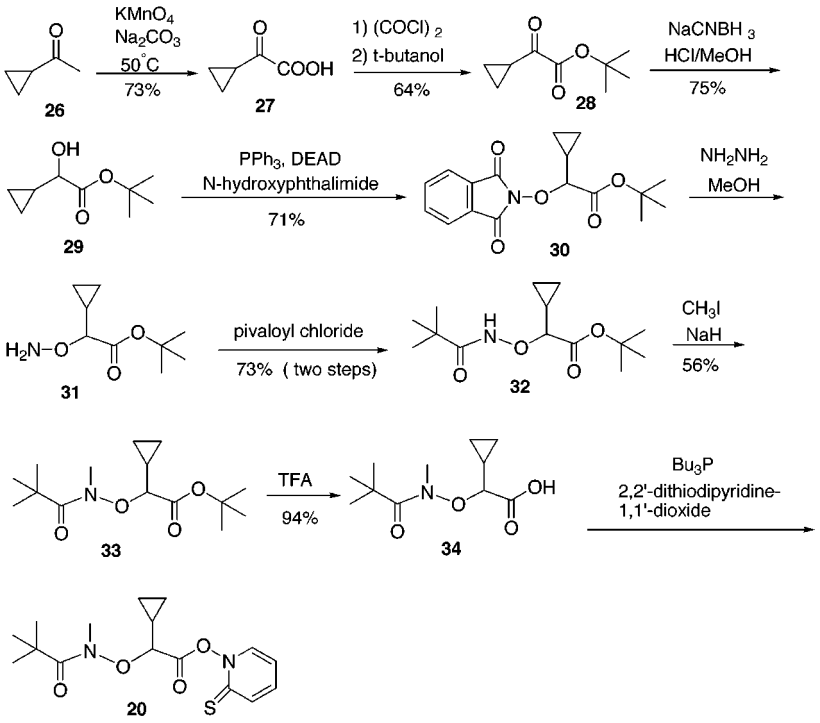
Scheme 3



was obtained for the photolysis of **20**. NMR analysis of the crude reaction mixture demonstrated that amide **19** and the phenyl-substituted analogue of **23** were the major products of the radical fragmentation reaction. However, several minor components in the vinylic region that did not correspond with the expected ring-opened compound were observed and additional experiments will be needed before this system can be used to calibrate the rate of the N−O bond fragmentation. While not allowing for a precise determination, this experiment demonstrates that the NO bond cleavage is competitive with the ring opening of the (2-phenylcyclopropyl)methyl radical ($k = 1.6 \times 10^{11}$ s^{-1}).[4]

The ring opening of the cyclopropyl carbinyl radical is the most widely used radical trap in mechanistic enzymology[3] and has been used for example to probe for radical intermediates in the reactions catalyzed by monoamine oxidase,[5] isopenicillin N synthase,[6] deacetoxyacetylcephalosporin C synthase,[7] methane monooxygenase,[8] cytochrome P450,[9] and acyl CoA dehydrogenase.[10] However, in many cases the addition of a cyclopropyl group or a phenyl-

Scheme 4



substituted cyclopropyl group to the substrate for an enzymatic reaction is too large a perturbation on the structure and such substrate analogues cannot bind at the active site of the enzyme.[11] In addition, the synthesis involved in the introduction of the cyclopropyl group into the substrate can be difficult. For such cases, the alkyl hydroxamate based radical probe described here may be a useful alternative.

Acknowledgment. This research was supported by a grant from the American Heart Association.

Supporting Information Available: The synthetic and photolytic procedures for compounds **12** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991392L

(8) Liu, K. E.; Johnson, C. C.; Newcomb, M.; Lippard, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 939.

(9) (a) Toy, P. H.; Newcomb, M.; Vaz, A. D. N.; Coon, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 9718. (b) Atkinson, J. K.; Hollenberg, P. F.; Ingold, K. U. Johnson, C. C.; Le Tadic, M. H.; Newcomb, M.; Putt, D. A. *Biochemstry* **1994**, *33*, 10630. (C) Atkinson, J. K.; Ingold, K. U. *Biochemstry* **1993**, *32*, 9209. (d) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5699.

(10) (a) Li, D.; Zhou, H.-Q.; Dakoji, S.; Shin, I.; Oh, E.; Liu, H.-W. *J. Am. Chem. Soc.* **1998**, *120*, 2008. (b) Lai, M.-T.; Li, D.; Oh, E.; Liu, H.-W. *J. Am. Chem. Soc.* **1993**, *115*, 1619. (c) Lai, M.-T.; Liu, H.-W. *J. Am. Chem. Soc.* **1992**, *114*, 3160.

(11) (a) Tandon, M.; Wu, M.; Begley, T. P.; Myllyharju, J.; Pirskanen, A.; Kivirikko, K. I. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1139. (b) Iwata-Reuyl, D.; Basak, A.; Silverman, L. S.; Engle, C. A.; Townsend, C. A. *J. Nat. Prod.* **1993**, *56*, 1373.