ORGANIC LETTERS

2006
Vol. 8, No. 24
5669−5671

Ceric Ammonium Nitrate Promoted Oxidation of Oxazoles

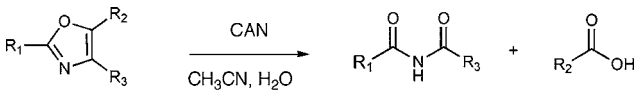
David A. Evans,* Pavel Nagorny, and Risheng Xu

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

evans@chemistry.harvard.edu

Received October 5, 2006

ABSTRACT



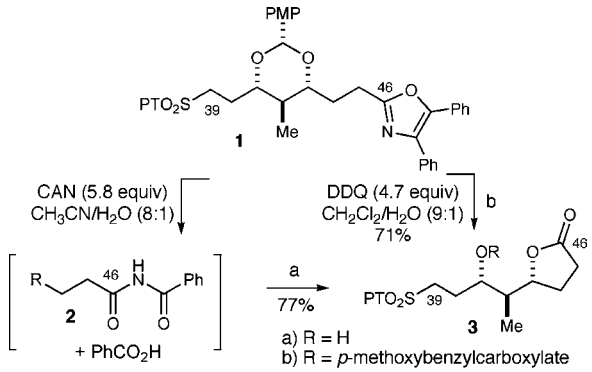
R_1, R_2, R_3 = Aryl, Alkyl, Alkenyl, Yield: 50–90%

The ceric ammonium nitrate promoted oxidations of 4,5-diphenyloxazoles and oxazoles with various substitution patterns have been investigated. This transformation results in the formation of the corresponding imide in good yield and tolerates a wide variety of functional groups and substituents on the oxazole moiety.

The selection of an appropriate protecting group in the context of a complex organic synthesis remains an ongoing challenge due to constraints arising from compatibility issues. In particular, finding a protecting group that is capable of preserving the carboxylic acid oxidation state can be especialy difficult. Although there are a number of protecting groups developed for alcohols, there are fewer options for masking a carboxylic acid, with esters[1] and amides[1,2] usually being the most common choices.

In our recent studies resulting in the total synthesis of oasomycin A,[3] we employed the "Wasserman option"[4] for this problem: the protection of the C_{46} lactone carboxylate of oasomycin A as its derived 4,5-diphenyloxazole. The singlet oxygen-mediated liberation of this carboxyl moiety could, in principle, be executed at numerous points in the synthesis due to the compatibility of this transformation with the multitude of other oxygen-protecting groups in the assembled or partially assembled subunits. The purpose of this paper is to report that this heterocycle is also quite sensitive to one-electron oxidants such as ceric ammonium nitrate (CAN) or DDQ. Thus, when oxazole **1** was exposed to these oxidants (Scheme 1), the corresponding lactones **3a**

Scheme 1. Oxidation of the Oasomycin A[a,b] $C_{39}-C_{46}$ Subunit



(PMP = *p*-methoxyphenyl, PT = 1-phenyl-1*H*-tetrazole).

and **3b** were obtained. Acordingly, these reagents provide an alternative to oxazole singlet oxygenation.

Examination of the CAN[5]-promoted oxidation leading to **3a** revealed that lactone **3a** is formed through the intermediacy of imide **2**. Intrigued by the fact that the 4,5-

(1) Green, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.

(2) For examples of amide protecting groups in organic synthesis, see: (a) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Engl.* **2002**, *41*, 4573−4576. (b) Evans, D. A.; Katz, J. L.; Peterson, G. S.; Hintermann, T. *J. Am. Chem. Soc.* **2001**, *123*, 12411−12413. (c) Evans, D. A.; Carter, P. H.; Carreirra, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540−7552 and references cited therein.

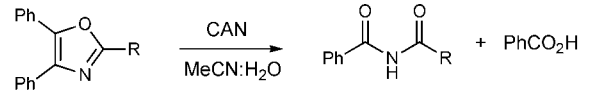
(3) Evans, D. A.; Nagorny, P.; Reynolds, D. J.; McRae, K. J. *Angew. Chem., Int. Ed.* **2006**, *45*, in press.

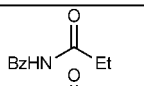
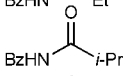
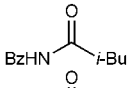
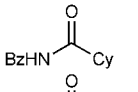
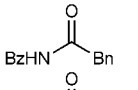
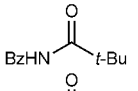
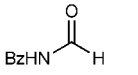
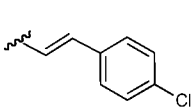
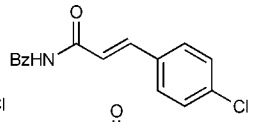
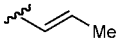
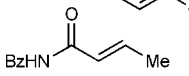
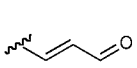
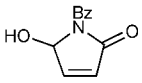
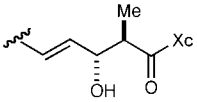
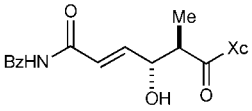
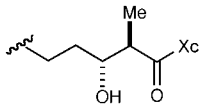
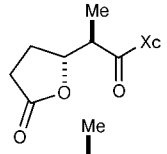
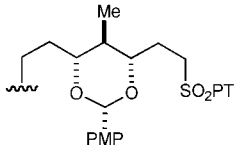
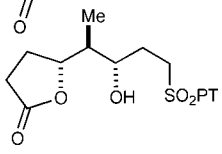
(4) (a) Wasserman, H. H.; DeSimone, R. W.; Ho, W. B.; Spencer-Prowse, K.; Spada, A. P. *Tetrahedron Lett.* **1992**, *33*, 7207−7210. (b) Wasserman, H. H.; Gambale, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 1423−1424 and references cited therein.

10.1021/ol0624530 CCC: $33.50
Published on Web 11/02/2006

diphenyloxazole moiety is oxidized in preference to the *p*-methoxybenzyl acetal, we decided to investigate the generality of this reaction. Thus, a CAN-mediated oxidation of a simple oxazole (entry 4) was executed under similar conditions (Table 1). The formation of a corresponding imide

Table 1. The Oxidation of Various 4,5-Diphenyloxazoles



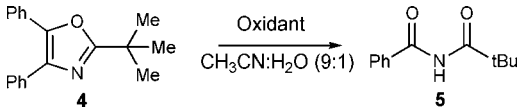
entry	R	product	yield
1[a]	Et		75%
2[a]	*i*-Pr		70%
3[a]	*i*-Bu		84%
4[a]	Cy		91%
5[a]	Bn		55%
6[a]	*t*-Bu		90%
7[a]	H		89%
8[a]			98%
9[a]			68%
10[a]			66%
11[b]			60%
12[b]			80%
13[c]			77%

[a] The reaction was carried out using 3.8 equiv of CAN in CH_3CN/H_2O (8:1), rt. [b] Reaction was carried out using 2.7 equiv of CAN in CH_3CN/H_2O (8:1), rt. [c] Reaction was carried out using 5.8 equiv of CAN in CH_3CN/H_2O (8:1), rt (Bz = benzoyl, PMP = *p*-methoxyphenyl, PT = 1-phenyl-1*H*-tetrazole, Xc = (*S*)-4-benzyloxazolidin-2-one).

was also observed, and it was optimal when more than 3.0 equiv of CAN was used. Eleven other 4,5-diphenyloxazoles have been evaluated (Table 1). The oxidation was found to be general, affording the corresponding imide and benzoic acid for a variety of substrates. The illustrated reaction is tolerant of primary, secondary, and tertiary alkyl substitution in the 2-position (entries 1−7)[6] as well as to alkenyl substitutents (entires 8−11).[6] In general, even in the complex cases (entries 11−13),[3] the 4,5-diphenyloxazole moiety was oxidized preferentially to the other functional groups. However, in cases where the substituent is prone to oxidation (entry 5) or the resulting imide can be isomerized (entries 10 and 11), an erosion of yield was observed. In the later cases (entries 12 and 13), the intermediate imide can be intercepted by a careful monitoring of the reaction progress. Thus, depending on the oxidation time (entry 13, Table 1), the transformation can afford either imide **2** or lactone **3a** (Scheme 1) in 76 and 77% yield, respectively.

Next, we decided to examine other one-electron oxidants that mght be used as alternatives to CAN. The results of this survey are outlined in Table 2. Potassium permanganate

Table 2. Survey of Different Oxidants



4 **5**

entry	oxidant	time (h)	yield (%)	side product (yield, %)
1	$KMnO_4$	2	57	benzil (24)
2	$Mn(OAc)_3$	336	0	
3	DDQ	336	0	benzil (<5)
4	DDQ[a]	336	0	
5	$Ce(OTf)_4$	48	40	benzil (<5)
6	$Ce(SO_4)_2$	48	0	benzil (42)
7	CAN	2	90	

[a] Performed in CH_2Cl_2/H_2O (9:1), rt.

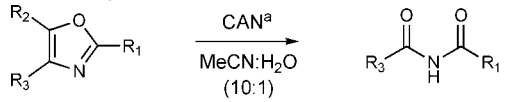
was found to promote the oxidation of **4** to the corresponding imide (entry 1); however, a lower yield as well as substantial amounts of the benzil side product made this oxidant less attractive. Manganese(III) acetate and DDQ (entries 2−4) did not exhibit any reactivity such that starting material and traces of benzil were the only detectable products. Interestingly, the fact that sulfone **1** was slowly oxidized with DDQ (Scheme 1) with the formation of lactone **3b** and benzil indicates that the C_{43} alcohol is essential for this transformation to take place. Finally, we decided to examine other Ce(IV) sources (entries 5 and 6). Thus, we found a solution of $Ce(SO_4)_2$ in sulfuric acid did not promote any reaction besides the minor hydrolysis of oxazole followed by oxidation of the formed benzoin to benzil. In contrast, $Ce(OTf)_4$ slowly oxidized oxazole **4** to the corresponding imide **5**.

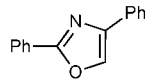
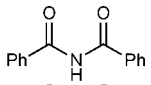
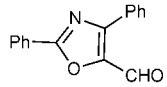
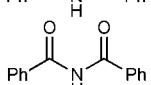
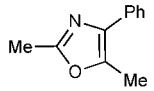
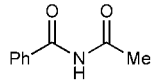
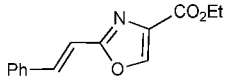
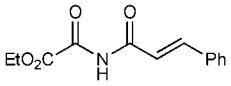
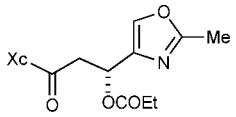
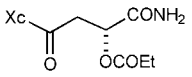
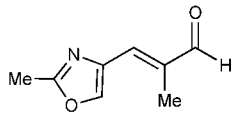
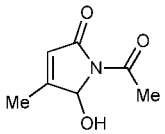
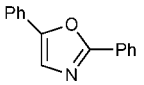
(5) For the reviews of CAN-promoted oxidations, see: (a) Dhakshinamoorthy, A. *Synlett* **2005**, *19*, 3014−3015. (b) Nair, V.; Balagopal, L; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21−30. (c) Nair, V.; Panicker, S. B.; Nair, L. G.; George, T. G.; Augustine, A. *Synlett* **2003**, *2*, 156−165. (d) Nair, V.; Mathew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997**, *26*, 127−132. (e) Molander, G. *Chem. Rev.* **1992**, *92*, 29−68.

(6) (a) Meanwell, N. A.; Rosenfeld, M. J.; Trehan, A. K.; Wright, J. J. K.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming, J. S.; Gamberdella, M.; Zavoico, G. B.; Seilert, S. M. *J. Med. Chem.* **1992**, *35*, 3483−3497. (b) Wasserman, H. H.; Gambale, R. J.; Pulmer, M. *Tetrahedron* **1981**, *37*, 4059−4067.

The CAN-promoted oxidation of other types of oxazoles has also been addressed (Table 3). In general, a variety of

Table 3. Survey of Substituted Oxazole Oxidation

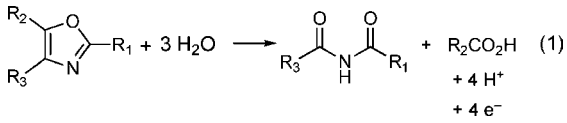


entry	substate	product	yield
1			95%
2			90%
3[b]			90%
4			93%
5			65%
6			55%
7		decomposition	–

[a] The reaction was carried out using 3.8 equiv of CAN in CH_3CN/H_2O (8:1). [b] Reaction was carried out using 3.3 equiv of CAN in CH_3CN/H_2O (8:1) (PMP = *p*-methoxyphenyl, PT = 1-phenyl-1*H*-tetrazole) Xc = (*R*)-4-benzyloxazolidin-2-one.

analogues (entries 1−5)[7] may be readily oxidized to the derived imides. Similar to 4,5-diphenyloxazoles, the corresponding imide could be isomerized or cleaved under the reaction conditions (entries 5−7). Also, the oxidation seems to be sensitive to the nature of the R_3 substituent, and in some cases, the oxidation was sluggish (entry 5) or resulted in decomposition of the starting material (entry 7).

The balanced half-reaction for the oxazole transformation requires a 4-electron oxidation (eq 1). While the electron source could be exclusively Ce(IV), nitrate reduction cannot be ruled out as an additional source of electrons.[8]



In conclusion, we have developed an efficient method of oxidizing oxazoles to the corresponding imides. This oxidation may serve as an alternative to the Wasserman singlet oxygen conditions if other functionalities sensitive to singlet oxygen are present. The fact that 4,5-diphenyloxazoles are stable to a number of different oxidants (Table 2) while being easily oxidized with CAN makes this functionality a useful protecting group for imides and carboxylic acids. Also, we believe that the awareness of such an oxidation is important in realizing the total syntheses of complex oxazole-containing natural products, as a number of modern oxidants are known to act via a one-electron-transfer mechanism.

Acknowledgment. Financial support has been provided by the National Institutes of Health (GM-33327-19).

Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0624530

(7) For the syntheses of the substrated of entries 3−6, see: (a) Nagayoshi, K.; Sato, T. *Chem. Lett.* **1983**, *9*, 1355−1356. (b) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1996**, *61*, 6496−6497. (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J.; Cho, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046. (d) Boger, D. L.; Curran, T. T.; *J. Org. Chem.* **1992**, *57*, 2235−2244.

(8) (a) Fujioka, H.; Ohba, Y.; Hirose, H.; Murai, K.; Kita, Y. *Org. Lett.* **2005**, *7*, 3303−3306. (b) Zhang, Y.; Jiao, J.; Flowers, R. A., II. *J. Org. Chem.* **2006**, *71*, 4516−4520.