Pergamon

Tetrahedron Letters 40 (1999) 6145–6148

TETRAHEDRON LETTERS

Singlet oxygen oxidation of pyrroles. Formation of 5-substituted derivatives

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Received 7 May 1999; accepted 9 June 1999

Abstract

The *tert*-butyl ester of 3-methoxy-2-pyrrolecarboxylic acid **3** undergoes reaction with singlet oxygen to form an intermediate imino hydroperoxide **4**. This hydroperoxide may be trapped by a variety of nucleophiles yielding 5-substituted pyrroles **6**. With strong nucleophilic substituents at the 5-position, these pyrroles may add to unreacted hydroperoxide **4** to form bipyrrole-like products **7**. © 1999 Elsevier Science Ltd. All rights reserved.

Oxidations of heterocyclic compounds by singlet oxygen are of special interest because of the involvement of many of these reactions in the toxic effect on living organisms associated with 'photodynamic action',[1] and also because of applications of these transformations in the synthesis of bioactive products.[2]

In many cases, the significance of these oxidations is limited by the lack of specificity in the reactions with the high energy singlet oxygen species. With pyrrole derivatives which have received extensive earlier study,[2,3] we have recently shown that when both electron-releasing and electron-attracting groups are substituted on the hetero ring, the oxidations may take place under more control. *N*-Alkylpyrroles such as **1** yield products derivable from zwitterionic intermediates of type **2**.[4] By contrast, *N*-unsubstituted pyrroles such as the 3-methoxy-2-carboxylate **3** appear to form intermediate hydroperoxides **4**,[5,6] which undergo addition–elimination reactions with nucleophiles (NuH) to yield 5-substituted derivatives. An earlier report describes how such 5-substituted pyrroles, in which the 5-substituent is an alkoxyl group, may act as reactive nucleophiles, adding in a second stage to the putative imino hydroperoxide to form bipyrrole-like derivatives **7**.[7]

We now report that the addition–elimination reactions of **4** take place with a variety of nucleophiles leading to the introduction of substituents at the 5-position of the pyrrole. The process is illustrated in Scheme 1, showing photooxidation leading to hydroperoxide **4**, which acts as an acceptor for reaction with other nucleophilic components. The nucleophile may be an alcohol used as solvent or another donor molecule such as piperidine, a proline ester, a heterocycle such as imidazole, a β-diketone such as acetylacetone, dimedone, or other cyclic 1,3-diketone. The results of our studies are summarized in Table 1.[10]

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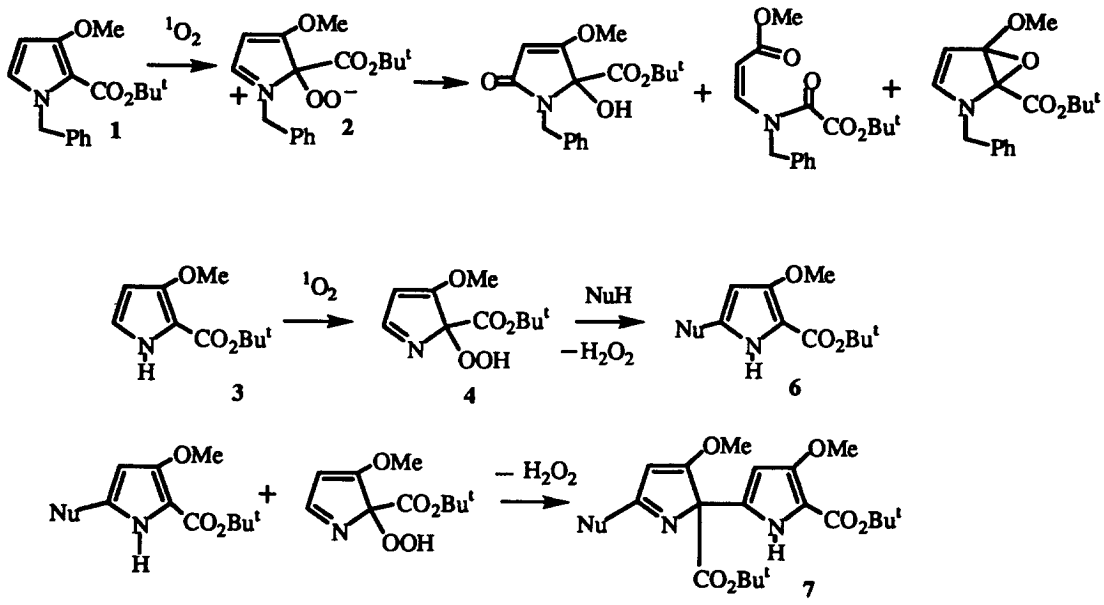
PII: S0040-4039(99)01171-5



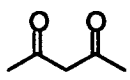
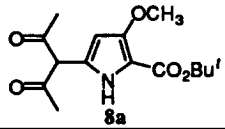
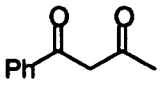
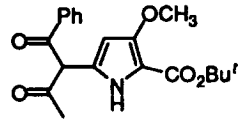
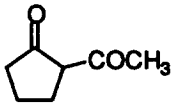
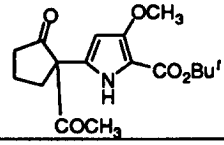
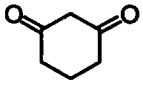
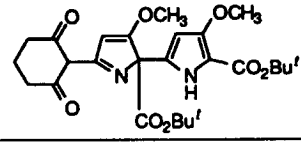
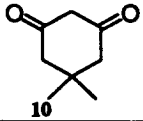
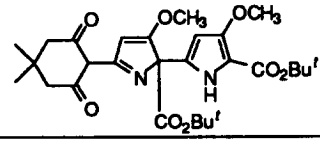
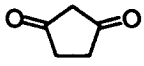
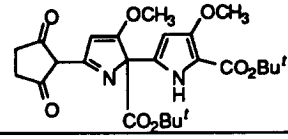
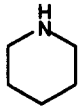
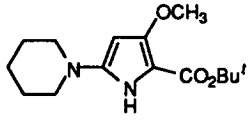
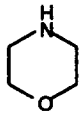
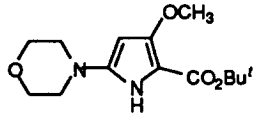
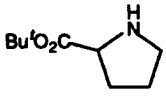
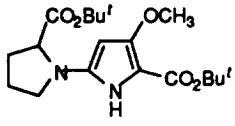
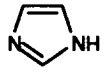
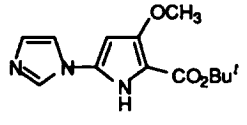
Scheme 1.

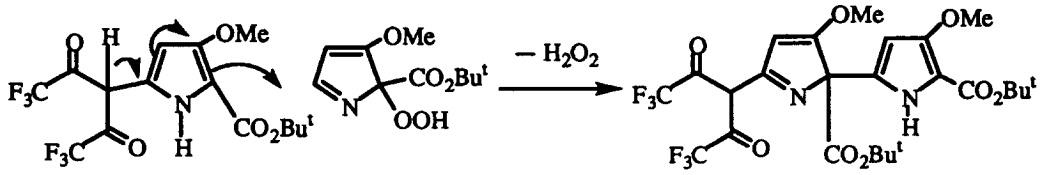
The following general procedure illustrates the reaction with acetylacetone **8**: A solution of *tert*-butyl 3-methoxy-1*H*-2-pyrrole carboxylate (20 mg, 0.10 mmol) in 25 mL of CH_2Cl_2 was cooled to –78°C and subjected to photooxygenation under irradiation with a 650 W tungsten lamp for 10 min in the presence of methylene blue as sensitizer. Acetylacetone (60 mg, 0.6 mmol) in CH_2Cl_2 (10 mL) was then added to the cold solution. This was stirred for 10 min, and then concentrated in vacuo. The residue was purified by preparative TLC using EtOAc:hexane (1:2) as eluant to give the product **8a** (23.3 mg, 78%) as a pale white solid. ^1H NMR ($CDCl_3$): 8.5 (b, 1H, NH), 5.79 (d, J=2.9 Hz, 1H), 3.86 (s, 3H), 1.99 (s, 6H), 1.57 (s, 9H). ^{13}C NMR ($CDCl_3$): 192.8, 160.2, 153.1, 128.3, 108.4, 106.3, 98.4, 80.8, 58.2, 28.4, 23.8. IR ($CHCl_3$): 3440, 3010, 2980, 1680, 1660 cm^{-1}. HRMS calcd for $C_{15}H_{21}NO_5$: M^+ 295.1420; found: 295.1412.

Our work has shown that depending on the nucleophile, both monoaddition, as well as second-stage addition to the hydroperoxide intermediate, may take place. When the reactions were run in alcoholic solvents, the alcohols acted as donor reagents forming 5-alkoxy pyrroles. As reported earlier,[7] these electron-rich adducts, which could be isolated under certain conditions, were capable of undergoing further addition to the iminohydroperoxide intermediate yielding bipyrrolic-like products.

It is interesting to note that the reaction of acetylacetone **8** (pKa=8.95) described above leads exclusively to monoaddition product, while the comparable reactions of the cyclic β-diketones, cyclohexanedione **9** (pKa=5.26), dimedone **10**, and cyclopentanedione **11** yielded only diaddition products. These results may be explained on the basis of the greater acidity of the cyclic β-diketones[8] enhancing the nucleophilic character of the first-formed 5-substituted derivatives and favoring the second-stage addition–elimination. In accord with this view we found that use of hexafluoroacetylacetone **12** (pKa=5.30)[9] as a nucleophile in the above low temperature oxidation sequence yielded the diaddition product **12a** as the only isolable species (Scheme 2). We are continuing studies on the conditions which distinguish between monosubstitution and the products of second-stage reaction. In a paper to follow, an application of this reaction to the synthesis of α,α′-bipyrrole products in the prodigiosin series is described.

Table 1
Reaction of $^1O_2$ with pyrrole **3** at –78°C. Trapping of peroxidic intermediate

Nucleophile	Monosubstitution Product	Secondary Addition Product	Yield,%
 **8**	 **8a**		78
			38
			48
 **9**			53
 **10**			78
 **11**			55
			33
			25
			30
			49



12a

Scheme 2.

Acknowledgements

This work was supported by grants from the National Institutes of Health and the National Science Foundation. The technical assistance of Ms. Guizhen Dong is gratefully acknowledged.

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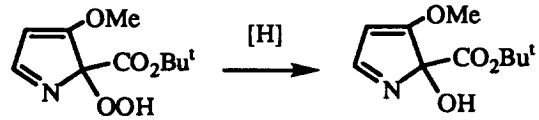
5. The hydroperoxide **4** is too reactive for isolation but could be identified by reduction of the $^1O_2$ reaction mixture at –78°C in CH_2Cl_2 with triethyl phosphite (Ref. 6). The product shows NMR and HRMS expected for the 2-hydroxy derivative **5**.



4 **5**

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10. All new products were characterized by IR, ^1H NMR, ^{13}C NMR and HRMS.