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# Pyrrole Photooxidation. A Pathway to Bipyrrolic Products.

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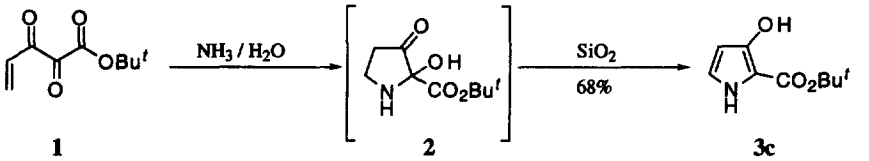
***Abstract:*** Dye-sensitized photooxidation of *tert*-butyl 3-methoxypyrrole-2-carboxylate in methanol yielded *tert*-butyl 3,5-dimethoxypyrrole-2-carboxylate and a bipyrrolic oxidative coupling product. A mechanism for the formation of the coupling product is presented. Copyright © 1996 Elsevier Science Ltd

The reactions of pyrroles with singlet oxygen continue to be of interest because of the widespread occurrence of pyrrolic systems in products of biological interest and because of their involvement in the destructive action associated with the so-called photodynamic effect.[1] In numerous studies on pyrroles with varied substitution, the main features of the singlet oxygen oxidation have been elucidated,[2,3,4,5,6] including the important influence of substituents, solvents, and other reaction conditions on the observed diversity of products. By contrast, aspects of these oxidations which have not been clarified are the processes leading to higher molecular weight products. These more complex materials have usually been observed in cases where the pyrroles under study are substituted with electron-releasing groups, rendering the heterocyclic rings more vulnerable to oxidation by the electrophilic singlet oxygen species.

In the present study, attention was focused on the singlet oxygen oxidation of *tert*-butyl 3-methoxypyrrole-2-carboxylate **6**, in which the nitrogen atom is unsubstituted. Earlier, we explored the dye-sensitized photooxidation of the corresponding *N*-alkyl compounds in methanol and were able to isolate products **5** derivable from the hypothetical intermediate zwitterion **4a** (Scheme 2). Based on previous experience with the oxidation of *N*-unsubstituted pyrroles by singlet oxygen, the $^1O_2$ reaction with **6** was expected to give a more complex mixture of products, most probably through the intermediate hydroperoxide **8**.

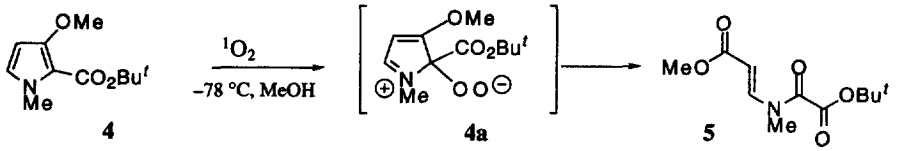
The synthesis of the starting *N*-unsubstituted pyrrole **3**[7] was accomplished by our general route to 3-hydroxypyrrole-2-carboxylates involving addition of ammonia or amines to the vinyl tricarbonyl compound **1** (Scheme 1).[8] *O*-Methylation of **3** took place with sodium hydride and dimethyl sulfate, forming **6**.[13]

While the reaction of the *N,O*-dimethyl derivative **4** with $^1O_2$ gave mostly **5** by 2,3-cleavage[3] (Scheme 2), the photooxygenation of pyrrole **6** took a completely different course. In methyl alcohol at -78 °C using methylene blue (MB) as sensitizer, oxygenation yielded the higher molecular weight product **11a** (Scheme 3). The assignment of structure **11a** was based on IR, $^1H$ NMR, $^{13}C$ NMR, and HRMS.[9]



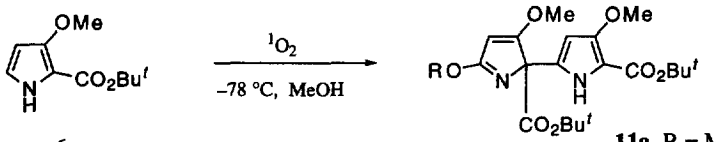

**1** **2** **3c**

Scheme 1




**4** **4a** **5**

Scheme 2

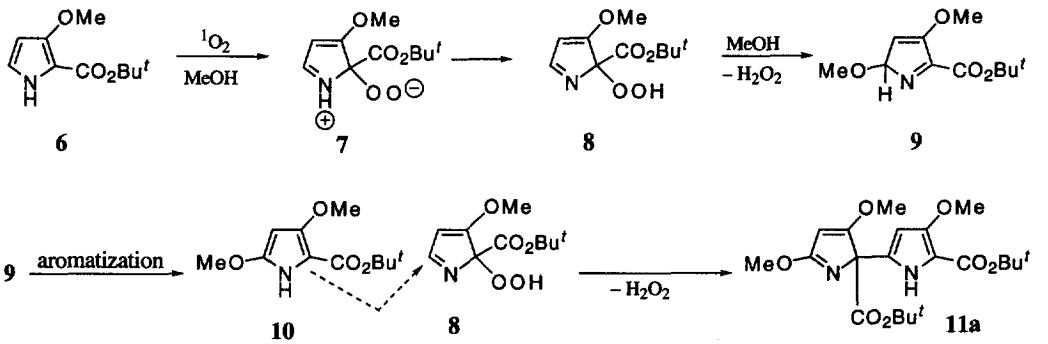



**6**

**11a** R = Me
**11b** R = Et

Scheme 3

We propose that the bipyrrole **11a** is formed by the mechanism outlined in Scheme 4, in which the initial addition of singlet oxygen forms the zwitterion **7** and then the hydroperoxide **8** by a proton shift. Addition of methanol to **8** accompanied by loss of hydrogen peroxide and aromatization yields the dimethoxypyrrole **10**.




**6** **7** **8** **9**

**10** **8** **11a**

Scheme 4

The electron-rich system **10** then adds to another molecule of hydroperoxide **8** in a second addition-elimination-aromatization process to yield **11a**. As expected from this process, substitution of ethanol for methanol forms the corresponding ethoxy derivative **11b**.

Precedent exists for the ready addition of pyrroles to pyrrolines, as in the addition of variously substituted pyrroles to 2-pyrroline reported by VanderWerf.[10] This reaction has been utilized by Rapoport[11] in a synthesis of the $\alpha,\alpha'$-bipyrrolic precursor of prodigiosin. In the present case, the opportunity for elimination-aromatization could well favor the coupling and permit the rapid reaction observed.

Additional support for the above mechanism was derived from an experiment in which the $^1O_2$ reaction was conducted in methanol under higher dilution (0.01 M). Under these conditions, the dimethoxypyrrole **10** was isolated (40%) along with 22% of the bipyrrole derivative **11a**. Identification of intermediate **10** was based on IR, HRMS and on the $^1$H NMR spectrum, clearly showing two methoxy peaks.

As in many examples of pyrrole photooxidation, reaction conditions such as dilution play a particularly important role in determining the nature of the products. Many examples of pyrrole-singlet oxygen reactions are known which normally lead to overoxidation and tar formation, but on dilution provide clean monooxidized products.[2,12] In this study, oxidation under dilute conditions generally gave higher yields of the bipyrrole derivative **11a**[14] as well as the 5-substituted intermediate **10**. We plan to continue studies on singlet oxygen reactions with pyrroles and other heterocyclic systems under dilute conditions in order to elucidate the relevant reaction pathways.

**Acknowledgments**

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## References and Notes

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9. TLC (EtOAc/hexanes = 1:1): $R_f$ 0.43; IR (KBr): 3440, 2970, 2920, 1735, 1700, 1665, 1630, 1565, 1478, 1445, 1380, 1365, 1275, 1250, 1215, 1150, 1100, 1010 cm[1]; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 9.00 (s (br), 1 H), 5.98 (d, $J$ = 2.97 Hz, 1 H), 5.13 (s, 1 H), 3.99 (s, 3 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 1.55 (s, 9 H), 1.43 (s, 9 H) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 178.8, 175.6, 166.6, 159.7, 152.9, 127.9, 107.3, 94.8, 92.1, 83.0, 80.1, 77.1, 59.6, 58.0, 55.0, 28.5, 27.7 ppm; HRMS (CI): *m/z* calculated for $C_{21}H_{31}N_2O_7$ $(M + H)^+$ 423.2136. Found 423.2131 (1 ppm).
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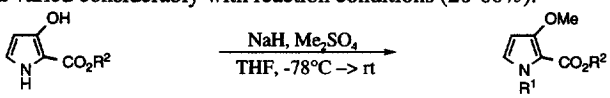
13. The *O*-methylated derivatives **4**,**6**,**12a**,**b** were readily prepared by treating the corresponding hydroxy pyrroles **3** with sodium hydride and dimethyl sulfate. However, in the reaction of the methyl (**3a**) and benzyl (**3b**) esters, both oxygen and nitrogen were methylated, forming *N*-methylpyrroles **12a** and **12b**, respectively. Only the *t*-butyl ester **3c** could be methylated exclusively at oxygen to give pyrrole **6**. Presumably the *t*-butyl group provides extra hindrance, preventing the nitrogen from being methylated under these conditions. An *N*,*O*-dimethylated derivative (**4**) could be obtained if higher temperatures were employed or if more than one equivalent of dimethyl sulfate was used.
14. The yields of **11a** varied considerably with reaction conditions (20-60%).




**3a** $R^2$ = Me
**3b** $R^2$ = Bn
**3c** $R^2$ = Bu$^t$

**4** $R^1$ = Me, $R^2$ = Bu$^t$, 48%
**6** $R^1$ = H, $R^2$ = Bu$^t$, 82%
**12a** $R^1$ = Me, $R^2$ = Me, 74%
**12b** $R^1$ = Me, $R^2$ = Bn, 96%

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