Pergamon

Tetrahedron Letters 40 (1999) 7587–7589

TETRAHEDRON LETTERS

Pyrrole-singlet oxygen reactions leading to α,α′-bipyrroles. Synthesis of prodigiosin and analogs

Harry H. Wasserman,* Anders K. Petersen, Mingde Xia and Jianji Wang

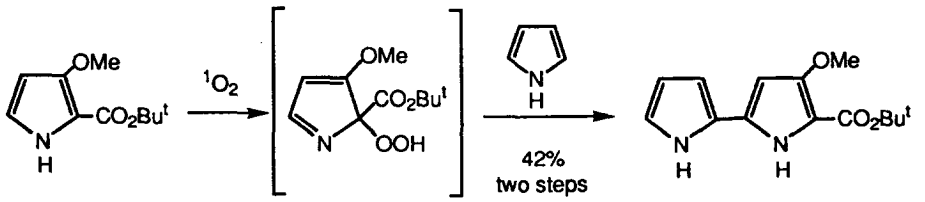
Department of Chemistry, Yale University, New Haven, CT 06520-8107, USA

Received 16 July 1999; revised 6 August 1999; accepted 7 August 1999

Abstract

Reaction of the *tert*-butyl ester of 3-methoxy-2-pyrrolecarboxylic acid with singlet oxygen yields a hydroperoxide intermediate which undergoes coupling with pyrroles to yield precursors of prodigiosin and ring A analogs, readily convertible to the corresponding tripyrromethenes.

We have recently reported that singlet oxygen oxidation of the *tert*-butyl ester of 3-methoxy-2-pyrrolecarboxylic acid (**1**) activates the pyrrole ring for substitution.[1,2] In this reaction taking place at −78°C, the oxidation of **1** by $^1O_2$ forms an intermediate imino hydroperoxide **2** which is not isolated, but may be trapped by a variety of nucleophiles to form 5-substituted pyrrole derivatives (Scheme 1).[2,3]



1 **2** **3**

Scheme 1.

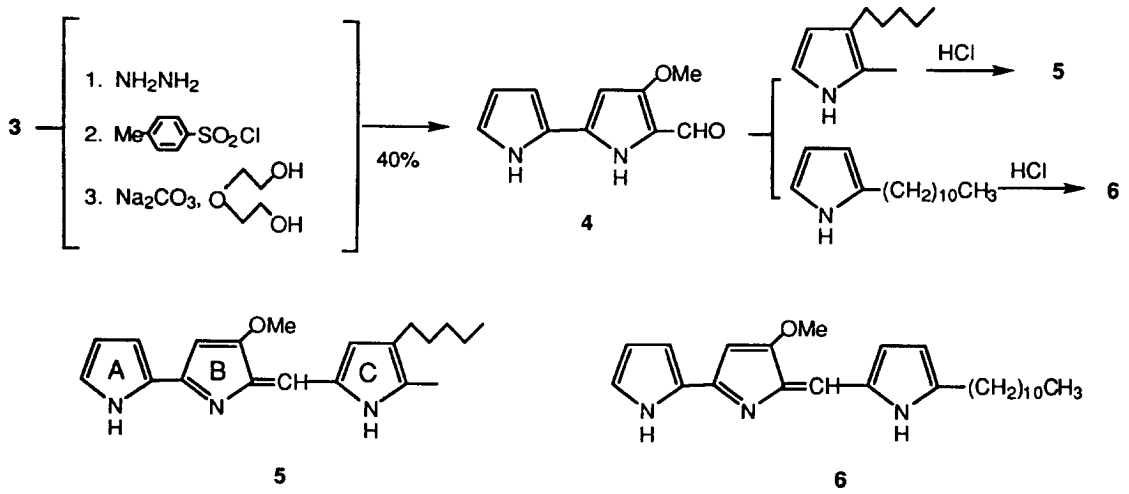
In the present communication we describe the use of this reaction to form α,α′-bipyrrole derivatives which are easily converted to tripyrromethenes including the natural product, prodigiosin **5**.[4,5] Ring **A** analogs of prodigiosin which have not been prepared by earlier routes are now readily accessible by this reaction sequence.

According to our procedure, the oxidation of **1** (20 mg, 0.1 mmol) in dichloromethane took place at −78°C in the presence of methylene blue in a stream of oxygen under irradiation with a 650w Sylvania tungsten halogen lamp.[2] After all of the starting material was consumed, a cold solution of pyrrole (33.5 mg, 0.5 mmol) in CH_2Cl_2 was added and the solution stirred for 1 h under N_2. The sensitizer was then removed by filtration and the solvent removed under reduced pressure. The product

* Corresponding author.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01538-5

(11 mg, 42%), purified by preparative TLC, shows ^{1}H and ^{13}C NMR spectra along with the HRMS corresponding to the α,α′-bipyrrole **3**. Bipyrrole **3** could be transformed to the prodigiosin precursor **4** by the McFadyen–Stevens reaction (Scheme 2).[5] The methoxy α,α′-bipyrrole aldehyde **4** thus formed (40%) was identical in all respects to the natural aldehyde isolated from a mutant strain of *Serratia*.[4b]

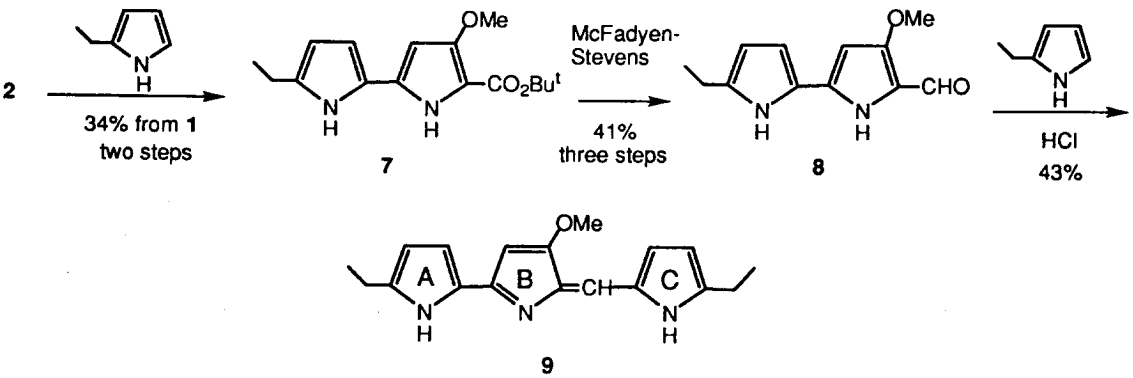


Scheme 2.

Interest in the synthesis of prodigiosin derivatives has recently been heightened with the finding that the parent natural product, prodigiosin **5**, shows potent antimicrobial and cytotoxic properties, although its use as a therapeutic agent is precluded by its high toxicity.[6] However, other members of this family, notably undecylprodigiosin **6**[7] have been reported to inhibit proliferation of T-cells at doses which are not cytotoxic.[8]

We viewed our procedure as a way of introducing the ring **A** pyrrole unit in the first stage of the tripyrromethene synthesis by using a substituted pyrrole as the nucleophilic component in the addition to the imino hydroperoxide. Accordingly, we carried out the singlet oxygen reaction as described above, adding 2-ethylpyrrole at low temperature to the peroxidic product. The α,α′-bipyrrole derivative which readily formed (34%) showed the spectroscopic properties expected for **7**.[9]

Formation of the tosyl hydrazide from **7** was followed by treatment with Na_2CO_3 according to the McFadyen–Stevens procedure yielding the ethyl-substituted methoxy α,α′-bipyrrole aldehyde **8** (Scheme 3).[9] Coupling of **8** with ethyl pyrrole in the presence of HCl yielded the prodigiosin analog **9** (43%).[9]



Scheme 3.

In summary, by application of the $^1O_2$-pyrrole reaction reported earlier, we have discovered a facile route to natural products in the prodigiosin family. In particular, our synthesis now readily permits the introduction of substituted pyrrole components as ring **A** units in the tripyrromethene framework. In our further work we are investigating the reactions of other heterocyclic systems[10] as nucleophiles in additions to the hydroperoxide **2**.

Acknowledgements

This work was supported by grants from the NIH and NSF. The technical assistance of Ms. Guizhen Dong is gratefully acknowledged.

References

1. Wasserman, H. H.; Power, P.; Petersen, A. K. *Tetrahedron Lett.* **1996**, *37*, 6657.
2. Wasserman, H. H.; Xia, M.; Wang, J.; Petersen, A. K.; Jorgensen, M. R. *Tetrahedron Lett.* **1999**, *40*, 6145.
3. Hydroperoxides related to compound **2** have been isolated from the methylene blue sensitized photooxidation of 2,5-di-*t*-butylpyrrole and 2,3,5-tri-*t*-butylpyrrole. Ramasseul, R.; Rassat, A. *Tetrahedron Lett.* **1972**, 1337.
4. (a) Wrede, F.; Rothhaas, A. *Z. Physiol. Chem.* **1934**, *95*, 226. (b) Wasserman, H. H.; McKeon, J. E.; Smith, L.; Forgione, P. *J. Am. Chem. Soc.* **1960**, *82*, 506.
5. (a) Rapoport, H.; Holden, K. J. *J. Am. Chem. Soc.* **1962**, *84*, 635. (b) Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405. (c) Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, *30*, 1725.
6. D'Alessio, R.; Rossi, A. *Synlett* **1996**, 513.
7. (a) Wasserman, H. H.; Rodgers, G.; Keith, D. D. *Chem. Comm.* **1966**, 825. (b) Harashima, K.; Tsuchida, N.; Tanaka, T.; Nagatsu, J. *Agr. Biol. Chem.* **1967**, *31*, 481. (c) Wasserman, H. H.; Rodgers, G. C.; Keith, D. D. *Tetrahedron* **1976**, *32*, 1851. (d) A recent synthesis of undecylprodigiosin reported by D'Alessio and Rossi[6] discloses a novel pathway to undecylprodigiosin by a Suzuki cross-coupling of two pyrrole rings.
8. Nakamura, A.; Nagai, K.; Ando, K.; Tamura, G. *J. Antibiotics* **1989**, *39*, 1155.
9. Spectroscopic data for selected compounds: Bipyrrole ester **7**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.81 (br, s, 1H), 10.64 (br, s, 1H), 6.40 (m, 1H), 6.09 (d, *J*=2.47 Hz, 1H), 5.76 (m, 1H), 3.71 (s, 3H), 2.55 (q, *J*=7.57 Hz, 2H), 1.48 (s, 9H), 1.18 (t, *J*=7.57 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz), δ 159.8, 153.2, 134.9, 128.7, 122.7, 106.3, 105.8, 105.3, 90.9, 78.5, 57.6, 28.3, 20.3, 13.8; IR (film) ν_{max} 3346, 3276, 2969, 1642 cm^{-1}; HRMS calcd for $C_{16}H_{22}N_2O_3$: 290.1630. Found: 290.1637. Anal. calcd for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64; N, 9.65. Found: C, 66.21; H, 7.60; N, 9.58. Bipyrrole aldehyde **8**: ^{1}H NMR (DMSO-d_6 500 MHz) δ 11.24 (br, s, 1H), 10.93 (br, s, 1H), 9.25 (s, 1H), 6.60 (m, 1H), 6.21 (2.43 Hz, 1H), 5. 83 (m, 1H), 3.82 (s, 3H), 2.57 (q, *J*=7.55 Hz, 2H), 1.18 (t, *J*=7.55 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.1, 158.7, 136.6, 133.5, 121.9, 117.1, 108.6, 106.1, 90.4, 57.7, 20.5, 13.7; IR (DMSO) ν_{max} 3450, 2960, 1603 cm^{-1}; HRMS calcd for $(M+H)^+$: 219.1133. Found: 219.1143. Prodigiosin analog **9** (HCl salt): ^{1}H NMR ($CDCl_3$ 500 MHz) δ 12.64 (br, s, 1H), 12.58 (br, s, 2H), 6.91 (s, 1H), 6.89 (dd, *J*=3.69, 2.47 Hz, 1H), 6.76 (dd, *J*=3.53, 2.51 Hz, 1H), 6.17 (d, *J*=3.53 Hz, 1H), 6.11 (dd, *J*=3.69, 2.10 Hz, 1H), 6.01 (d, *J*=1.55 Hz, 1H), 3.99 (s, 3H), 2.95 (q, *J*=7.60 Hz, 2H), 2.80 (q, *J*=7.64 Hz, 2H), 1.37 (t, *J*=7.60 Hz, 3H), 1.34 (t, *J*=7.64 Hz, 3H); ^{13}C ($CDCl_3$, 125 MHz), δ 166.1, 152.7, 148.7, 146.8, 127.8, 125.9, 122.0, 120.9, 119.5, 114.9, 111.2, 110.3, 92.8, 58.7, 21.7, 21.6, 13.5, 13.3; IR ($CHCl_3$) ν_{max} 3188, 3010, 2962, 1623 cm^{-1}; HRMS calcd for $(M+H)^+$: 296.1763. Found: 296.1760.
10. Recent work on the incorporation of a thiophene residue in the framework of a prodigiosin analog has been reported: Blake, A. J.; Hunter, G. A.; McNab, H. *J. Chem. Soc., Chem. Commun.* **1990**, 734.