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

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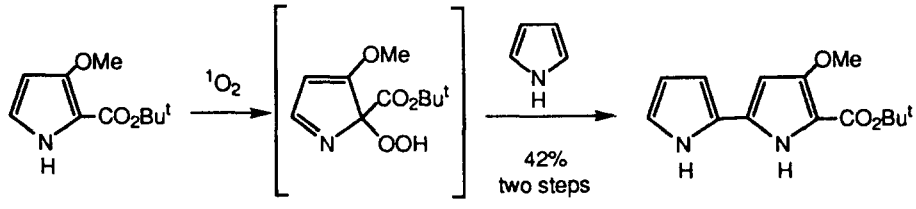
Abstract

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

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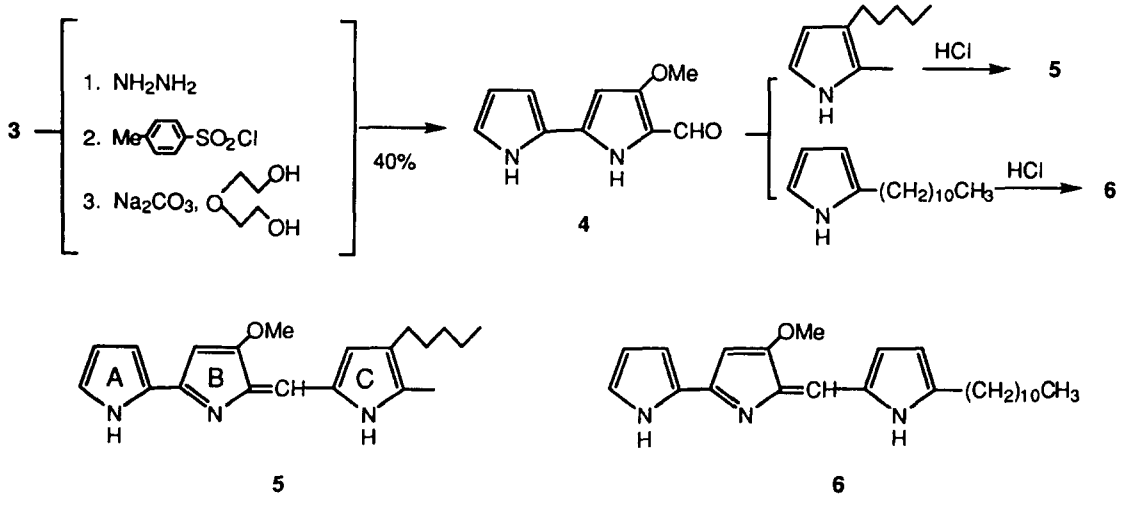
(11 mg, 42%), purified by preparative TLC, shows ^{1}H and ^{13}C NMR spectra along with the HRMS corresponding to the α,α′-bipyrrole **3**. Bipyrrole **3** could be transformed to the prodigiosin precursor **4** by the McFadyen–Stevens reaction (Scheme 2).[5] The methoxy α,α′-bipyrrole aldehyde **4**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

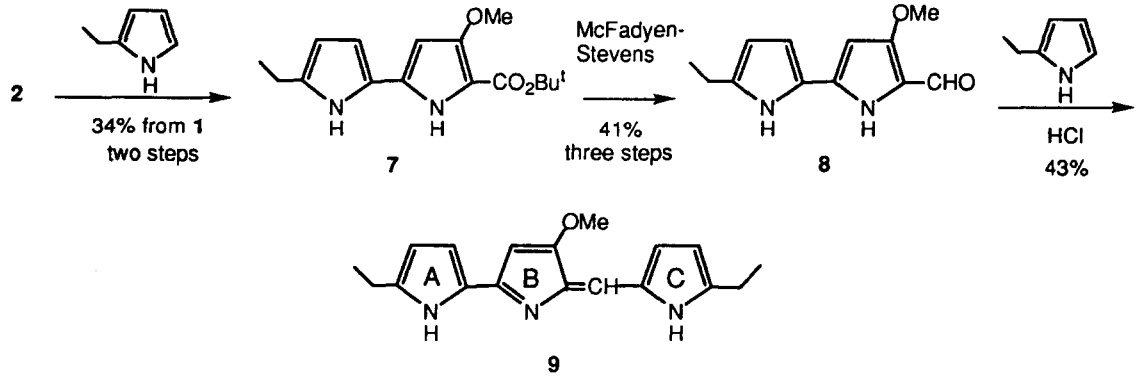


Scheme 2.

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

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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.
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