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Baeyer-Villiger Rearrangement of a Substituted Pyrrole by Oxone

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Abstract

Pyrroloxyls have been reported to exhibit very narrow EPR spectral lines, essential for *in vivo* imaging. En route to pyrroloxyls, we observed an unexpected Baeyer-Villiger rearrangement, leading to loss of aromaticity and formation of a 4,5-dihydro-1*H*-ketopyrrole.

Keywords

pyrrole; pyrroloxyl; Vilsmeier-Haack; Baeyer-Villiger

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Supplementary Information Detailed experimental procedures and compound characterization data are available as Supplementary Information in the online version.

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Introduction

The advent of low-frequency electron paramagnetic resonance (EPR) spectrometers¹ that can detect and image paramagnetic species in animals in real time creates an urgent need to synthesize stable free radicals (so-called “spin probes”) that can report *in vivo* physiology (e.g., O₂ concentration in various tissues).² Owing to their relative ease of synthetic manipulation, nitroxides are attractive as spin probes for physiological EPR spectroscopy and imaging.³

The utility of nitroxides as EPR imaging probes has been limited by their relatively large spectral linewidth (~1 G), which impacts both imaging sensitivity and spatial resolution. In 1970, Ramasseul and Rassat⁴ described the synthesis of pyrroloxyls that exhibited narrow EPR spectral linewidths in deoxygenated organic solvents (linewidth of one deuterium-substituted pyrroloxyl was reported to be ~0.1 G⁵). In view of their remarkable narrow linewidths, we wished to investigate the potential of pyrroloxyls as *in vivo* EPR imaging agents. For our initial series of studies,⁶ we decided to prepare 2,5-di-*tert*-butyl-3-ethoxycarbonyl-1-pyrroloxyl **5a**, using methods described by Ramasseul and Rassat.⁴ To our surprise, nickel peroxide oxidation of **4** afforded two products, neither of which was described by Ramasseul and Rassat: (a) 2,5-di-*tert*-butyl-3-ethoxycarbonyl-4-hydroxy-1-pyrroloxyl **5b**, which is readily oxidized to nonparamagnetic **7** and (b) the biradical 2,2',5,5'-tetra(*tert*-butyl)-4,4'-bis(ethoxycarbonyl)-3,3'-bipyrrolyl-1,1'-dioxyl **6** (Scheme 1).⁶ Despite the enhanced stability of biradical **6** as compared to pyrroloxyl **5b**, its dimeric nature makes it less than optimal as a contrast agent for *in vivo* EPR imaging. We therefore sought alternative nitroxides that might exhibit narrow EPR spectral lines. We decided to investigate the synthesis of more water-soluble analogs of the reported pyrroloxyls⁴ with the expectation that they would also exhibit narrow linewidths.

Results and Discussion

Based on our earlier publication,⁶ it is clear that all positions on the pyrrole ring must be substituted prior to the one-electron oxidation of N–OH to N–O•. We considered that preparation of di-ester **8**, followed by cyclization with hydroxylamine would afford the desired pyrrole **9** (Scheme 2). A careful review of the literature⁵ revealed that **9** was indeed accordingly obtained, but only in about 5% yield. In our hands, however, attempts to prepare **9** in an identical fashion were unsuccessful.

An alternative approach was sought. We reasoned that since **4** can be readily prepared in reasonable yield,^{4,6} initial protection of the N–OH followed by the Villsmeier-Haack reaction might result in the corresponding formylpyrrole **11**. Oxidation of **11**, followed by removal of the protective group, should lead to **9**. However, after *O*-benzylation of **4** to yield **10**, classic Villsmeier-Haack reaction conditions⁷ did not result in formylation (only **10** was recovered). By optimizing reaction conditions—1 equivalent of **10** in 5 equivalents of *N*-methyl-*N*-phenylformamide/ POCl₃ (solvent-free), 50°C, 3 h, followed by hydrolysis with aqueous sodium acetate—we obtained **11** in acceptable yield (Scheme 3).

While there are various methods for oxidizing aldehydes to acids and esters, the recent procedure of Travis, *et al.*,⁸ wherein Oxone[®] was used to convert aryl aldehydes to the corresponding ethyl esters, seemed an attractive approach to pyrrole **12**. One potential problem was that electron-rich molecules, such as 4-hydroxybenzaldehyde, can also undergo the Baeyer-Villiger reaction, resulting in a formate ester, which upon hydrolysis leads to the corresponding phenol.⁸ Because pyrrole **11** is not electron-rich, we were optimistic that the mild experimental conditions described in Travis, *et al.*,⁸ might favor oxidation to the desired ester and not a Baeyer-Villiger rearrangement.

When **11** and Oxone[®] (2:1 molar ratio of KHSO₅ to substrate) were stirred in absolute ethanol at room temperature for 16 h, no reaction occurred. When the ratio of KHSO₅ to **11** was increased to 6, and the reaction was vigorously stirred at room temperature for 3 days, TLC analysis indicated the formation of a new compound. The ¹H-NMR spectrum of the isolated product showed multiple resonances inconsistent with the highly symmetrical structure of **12**. The X-ray crystallographic structure⁹ of the isolated product revealed a rearrangement of **11** by Oxone[®], resulting in **13** rather than the predicted pyrrole **12** (Scheme 4). The presence of a chiral center in **13** implies the generation of stereoisomers. Indeed, **13** crystallizes as a racemate, with an asymmetric unit comprising a pair of enantiomers (Fig. 1).

We speculated that **11** could have undergone a Baeyer-Villiger-type oxidation mediated by Oxone[®], with subsequent rearrangement to **13**. To gain further insight into the mechanism underlying the formation of **13**, we changed experimental conditions to avoid using a protic solvent that could act as a nucleophile: reaction with 3 molar equivalents of Oxone[®] in DMF for 16 h at room temperature transformed **11** into a new product, **16**. The ¹H-NMR spectrum of **16** suggested the presence of a formate ester. The structure of **16** was determined by X-ray crystallography (Fig. 2),¹⁰ and is seen to be the formate ester expected from Baeyer-Villiger oxidation of **11** (Scheme 5).

Oxone is an acidic triple salt comprising potassium peroxymonosulfate, potassium hydrogen sulfate, and potassium sulfate (2KHSO₅·KHSO₄·K₂SO₄). Therefore, if formate ester **16** did form in the ethanolic Oxone reaction, acid-catalyzed transesterification with ethanol could have removed the formyl group to yield a hydroxypyrrole which, in turn, could have undergone rearrangement to yield the dearomatized compound **13**. To investigate this possibility, formate ester **16** was vigorously stirred with a mixture of anhydrous KHSO₄ and Na₂SO₄ in absolute ethanol at room temperature for 40 h. The sole isolated product was hydroxypyrrole **17** (Scheme 6). Thus cleavage of the formyl group did not trigger subsequent rearrangements under acidic, non-oxidizing conditions in anhydrous ethanol. In view of the last finding, we surmise that in the presence of Oxone in ethanol, formate ester **16** and/or hydroxypyrrole **17** must undergo further oxidative dearomatization and addition to generate pyrrolinone **13**.

To our knowledge, this is the first time that a hindered and fully substituted pyrrole has undergone a Baeyer-Villiger reaction to yield a product which, in the presence of an appropriate solvent, rearranges with loss of aromaticity. Attempts to oxidize **13** to the corresponding nitroxide using typical oxidants such as *m*-chloroperbenzoic acid, hydrogen

peroxide/sodium tungstate and dimethyldioxirane^{11,12} all failed, presumably owing to **13** being highly hindered.¹¹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- Single-crystal structure of **16**: C₂₃H₃₁NO₅, $M_r = 401.49$, $T = 150(2)$ K, triclinic, space group $P1$, $a = 10.1671(7)$ Å, $b = 11.1975(7)$ Å, $c = 11.4168(7)$ Å, $\alpha = 66.6953(9)^\circ$, $\beta = 65.9741(9)^\circ$, $\gamma = 73.5494(10)^\circ$, $V = 1078.68(12)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.236$ g·cm⁻³, $\mu = 0.086$ mm⁻¹, 10680 reflections (4244 independent, $R_{\text{int}} = 0.0146$), data/restraints/parameters 4244/0/300, goodness-of-fit on F^2 1.000, $R[F^2 > 2\sigma(F^2)] = 0.042$, $wR(F^2) = 0.086$, $\rho_{\text{max}} = 0.38$ e Å⁻³, $\rho_{\text{min}} = -0.22$ e Å⁻³. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre (Deposition number CCDC 993030).
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Figure 1. Enantiomers of **13** constituting the asymmetric unit in the X-ray crystallographic structure.⁹

Figure 2.
Formate ester **16** formed from Baeyer-Villiger oxidation of **11**.

Scheme 1.a) NaOEt, b) NH_2OH , c) NiO_2 , d) O_2

Scheme 2.a) Na/Et₂O, b) NH₂OH

Scheme 3.

a) Bn-Br, K₂CO₃, DMSO (70% yield); b) HCON(CH₃)C₆H₅/POCl₃ (47% yield). Bn = benzyl

Scheme 4.

a) Oxone/EtOH (48% yield). Bn = benzyl

Scheme 5.

a) Oxone/DMF (65% yield). Bn = benzyl.

Scheme 6.

Conditions: KHSO_4 , Na_2SO_4 , EtOH (62% yield). Bn = benzyl