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Baeyer–Villiger rearrangement of a substituted pyrrole by Oxone

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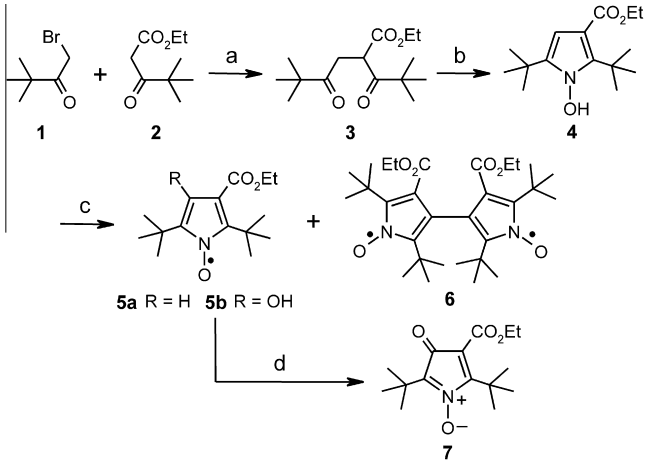
ABSTRACT

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.

Introduction

The advent of low-frequency electron paramagnetic resonance (EPR) spectrometers[1] 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., O_2 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 Rassat[4] 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 G[5]). 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



Scheme 1. Reagents and conditions: (a) NaOEt, (b) NH_2OH, (c) NiO_2, (d) O_2.

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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 pyrroloxyls[4] 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 literature[5] 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.

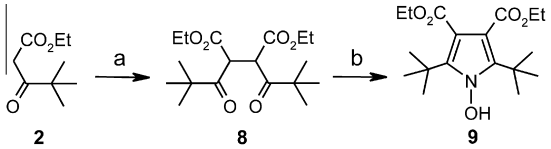
An alternative approach was sought. We reasoned that since **4** can be readily prepared in reasonable yield,[4,6] initial protection of the N–OH followed by the Vilsmeier–Haack reaction might result in the corresponding formylpyrrole **11**. Oxidation of **11**, followed by removal of the protective group, should lead to **9**. However, after O-benzylation of **4** to yield **10**, classic Vilsmeier–Haack reaction conditions[7] did not result in formylation (only **10** was recovered). By optimizing reaction conditions—1 equiv of **10** in 5 equiv of *N*-methyl-*N*-phenylformamide/$POCl_3$ (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.

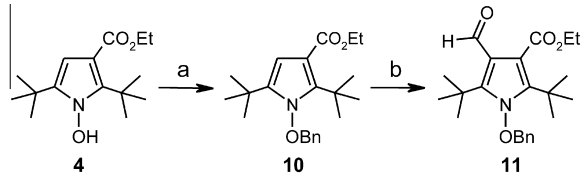
When **11** and Oxone® (2:1 molar ratio of $KHSO_5$ to substrate) were stirred in absolute ethanol at room temperature for 16 h, no reaction occurred. When the ratio of $KHSO_5$ to **11** was increased to 6, and the reaction was vigorously stirred at room temperature for 3 days, TLC analysis indicated the formation of a new compound. The ^{1}H NMR spectrum of the isolated product showed multiple resonances inconsistent with the highly symmetrical structure of **12**. The X-ray crystallographic structure[9] 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 ^{1}H 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).

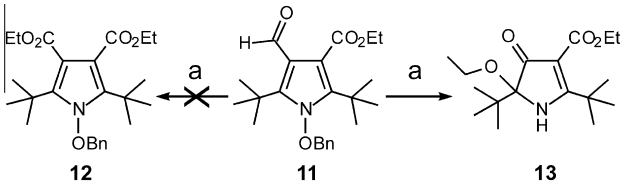
Oxone is an acidic triple salt comprising potassium peroxymonosulfate, potassium hydrogen sulfate, and potassium sulfate ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$). Therefore, if formate ester **16** did form in the ethanolic Oxone reaction, acid-catalyzed transesterification



Scheme 2. Reagents and conditions: (a) Na/Et_2O, (b) NH_2OH.



Scheme 3. Reagents and conditions: (a) Bn–Br, K_2CO_3, DMSO (70% yield); (b) $HCON(CH_3)C_6H_5/POCl_3$ (47% yield). Bn = benzyl.



Scheme 4. Reagents and conditions: (a) Oxone/EtOH (48% yield). Bn = benzyl.

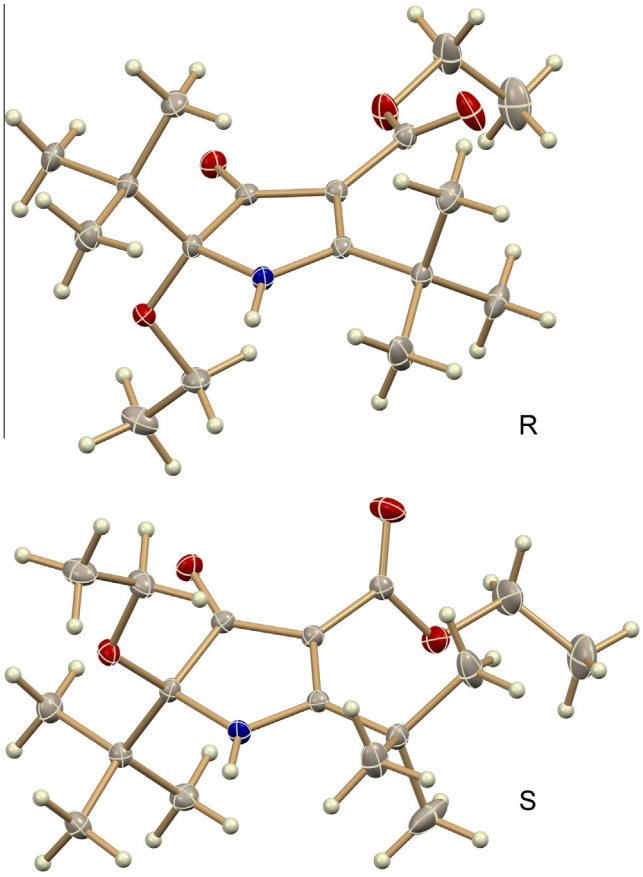


Figure 1. Enantiomers of **13** constituting the asymmetric unit in the X-ray crystallographic structure.[9]

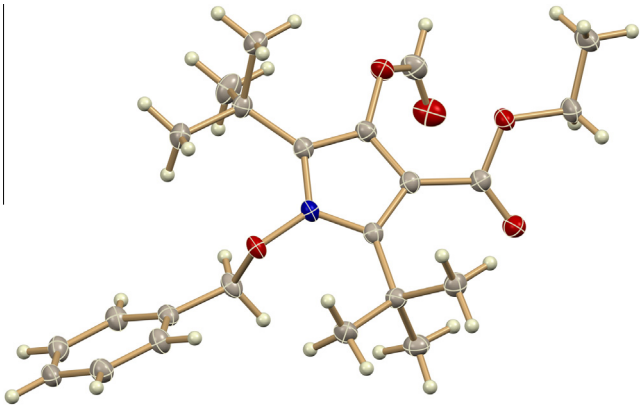
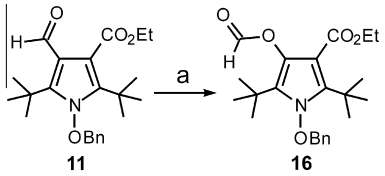
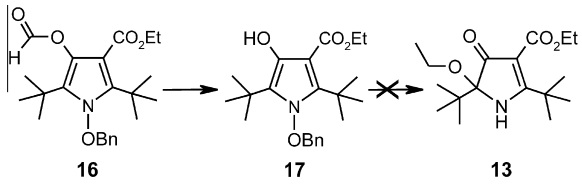


Figure 2. Formate ester **16** formed from Baeyer–Villiger oxidation of **11**.



Scheme 5. Reagents and conditions: (a) Oxone/DMF (65% yield). Bn = benzyl.



Scheme 6. Reagents and conditions: $KHSO_4$, Na_2SO_4, EtOH (62% yield). Bn = benzyl.

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 $KHSO_4$ and Na_2SO_4 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]

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Supplementary data

Supplementary data (detailed experimental procedures and compound characterization data are available as Supplementary Information in the online version.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet. 2014.04.004.

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10. *Single-crystal structure of* **16**: $C_{23}H_{31}NO_5$, M_r = 401.49, T = 150(2) K, triclinic, space group $P\bar{1}$, a = 10.1671(7) Å, b = 11.1975(7) Å, c = 11.4168(7) Å, α = 66.6953(9)° β = 65.9741(9)° γ = 73.5494(10)° V = 1078.68(12) Å^3, Z = 2, ρ_{calcd} = 1.236 g cm^{-3}, μ = 0.086 mm^{-1}, 10680 reflections (4244 independent, R_{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, $\Delta\rho_{max}$ = 0.38 e Å^{-3}, $\Delta\rho_{min}$ = −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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