Attempted Synthesis and Unexpected β -Fragmentation of a Hindered β -Keto Nitroxide.

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The attempted synthesis of a β -keto imidazolidinone nitroxide by oxidation of the β -hydroxy imidazolidinone precursor with hydrogen peroxide and sodium tungstate led to an unexpected ring-opening reaction to produce 1,4-diazaspiro[4.5]dec-1-en-3-oxo-2-pentanoic acid 1-oxide (**13**) in high yield. The structure of **13** was confirmed by X-ray crystallographic analysis. A β -fragmentation mechanism is suggested for the oxidative ring-opening reaction.

Introduction

There has been enormous world-wide interest in nitroxide-mediated polymerisation (NMP) following the discovery by the CSIRO that a pseudo-living type of control is possible in free radical systems using nitroxide-based initiators.^[1]

Imidazolidinone nitroxides such as **1** (R = Me) have been found to offer significant advantages over many of the nitroxides previously employed in nitroxide-mediated polymerization such as TEMPO, **2**, and the isoindoline nitroxide **3**. Block copolymers of styrene for example can be synthesized with controlled molecular weight, narrow molecular weight distribution, and defined end group functionality. Imidazolidinone nitroxides are synthesized from readily available precursors by a simple experimental route.^[2]

We were interested in preparing imidazolidinone nitroxides bearing a ketone adjacent to the nitroxide moiety, as this polar group might confer favorable properties on

the nitroxide in NMP, such as allowing polymerization at lower temperatures ($< 100\text{ }^{\circ}\text{C}$) or providing polymers of lower polydispersities, but it would also provide the opportunity to modify the steric environment around the nitroxide (by conversion to a cyclic acetal for example). There have been very few well-characterised and isolable β -keto-nitroxides reported. One example is the chiral nitroxide **4** (Figure 1) prepared in 3% yield via a 6-step synthesis from (1R)-(-)-10-camphorsulfonic acid.^[3]

Figure 1 Nitroxides useful in NMP and a β -keto-nitroxide

Our target molecule was the nitroxide **9** and the planned 3-step synthetic route is outlined in Scheme 1. There is good literature precedent for the conversion of **5** to nitroxide **8**. For example, cyclohexanone can be converted into nitroxide **1** ($R = H$) in high overall yield.^[4,5]

Scheme 1 Planned synthetic route to β -ketonitroxide **9**

Similarly, there is good literature precedent for the *in-situ* oxidation of the hydroxynitroxide **8** into the β -ketonitroxide **9** as nitroxides are well known to catalyse the oxidation of alcohols to carbonyl compounds.^[6,7,8]

Results and discussion

2-Hydroxycyclohexanone **5** was converted into hydroxyaminonitrile **6** in 76% yield. Condensation of **6** with cyclohexanone gave the expected hydroxyl imidazolidinone **7** in 50% yield. However, upon treatment of **7** in acetic acid with hydrogen peroxide and a catalytic amount of sodium tungstate at 20 °C, the product isolated was not the expected bis-spiro nitroxide **9**, but the ring-opened product **13**, which was formed in high (86%) yield. It is possible that the β -ketonitroxide **9** is formed initially but undergoes a Baeyer-Villiger rearrangement with peracetic acid ($\text{H}_2\text{O}_2 + \text{HOAc}$) to form the lactone followed by ring-opening. However, formation of **13** would require a final reduction of the lactone nitroxide to the lactone hydroxylamine, and this seems unlikely in the presence of excess H_2O_2 , especially given the high yield of **13**.

We believe that a more likely mechanism is via a β -fragmentation reaction as outlined in Scheme 2 (**12** $\rightarrow$ **13**). It is proposed that **7** undergoes the expected oxidation to give the nitroxide **8**, which can disproportionate in the presence of acid to give the oxoammonium species **10** and the corresponding hydroxylamine. Acid-catalysed disproportionation of nitroxides is well known.^[9] A mechanism is suggested in Scheme 2 (box). Protonation of the nitroxide followed by radical coupling with a second nitroxide could give either **14** or **15**, both of which can undergo fragmentation to give the hydroxylamine **16** and the oxoammonium species **17**. In the presence of an oxidizing agent, the hydroxylamine can be oxidized back to the nitroxide.

The oxoammonium species **10** can oxidise the neighbouring alcohol to the ketone **11**. Theoretical calculations (DFT) support an electrophilic attack by the oxoammonium moiety on the C-H α bond of the alcohol.^[10] An intramolecular mechanism is suggested in Scheme 2, but the reaction could be intermolecular. Reaction of the ketone **11** with peracetic acid would give an equilibrium concentration of the hemiacetal **12**, which would be expected to undergo a facile β -fragmentation to give the ring-opened carboxylic acid **13** directly.

Scheme 2. Suggested mechanism of formation of **13**.

Alternatively, the oxoammonium species **10** could undergo a cyclic ring-opening reaction to give the protonated nitronium **18**. The pendant aldehyde of **18** would be rapidly oxidised to the carboxylic acid under the reaction conditions (we thank a reviewer for this suggestion).

The structure of the carboxylic acid **13** was determined by mass spectrometry, ^1H and ^{13}C NMR and infrared spectroscopy. It has been reported previously, but was prepared by a quite different route^[11] and characterized only by a rather poor microanalysis and a melting point (164-166 °C) that differed significantly from the one reported here (139-140 °C). We have therefore confirmed the structure of **13** by X-ray crystallography (Figure 2).

Figure 2. X-ray structure of **13**

Conclusion

The attempted synthesis of the β -ketonitroxide 7,14-diazadispiro[5.1.5.2]pentadecan-9,15-dione-7-yloxy (**9**) by oxidation of 9-hydroxy-7,14-diazadispiro[5.1.5.2]pentadecan-15-one (**7**) led to an unexpected ring-opening reaction to produce 1,4-diazaspiro[4.5]dec-1-en-3-oxo-2-pentanoic acid 1-oxide (**13**) in high yield. The structure of **13** was confirmed by X-ray crystallographic analysis. A β -fragmentation rather than a Baeyer-Villiger mechanism accounts for the formation of **13** from **7**.

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The authors declare no conflicts of interest.

Experimental

General

All reagents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on a Varian UNITY-400 or a Varian Gemini

200 spectrometer. Chemical shifts are referenced to TMS (^1H and ^{13}C) unless otherwise stated, and J values are given in Hz. Melting points were determined by the capillary method and are uncorrected. Mass spectra were run on a VG Platform II mass spectrometer, coupled to a MassLynx data system. IR spectra were recorded on a Thermo Nicolet-Nexus FTIR apparatus.

1-Amino-2-hydroxy-cyclohexanecarbonitrile 6

Sodium cyanide (0.27 g, 5.44 mmol), ammonium chloride (0.35 g, 6.49 mmol) were added to ammonium hydroxide solution (100 mL) and allowed to dissolve over 20 min. 2-Hydroxycyclohexanone (0.5 g, 4.38 mmol) was added to the reaction mixture which was stirred for 3 days. The reaction mixture was extracted with DCM (400 mL), dried (MgSO_4), filtered and concentrated *in vacuo* to give the corresponding hydroxyaminonitrile **6** (0.47 g, 76% yield) as a white solid, mp 98-100 °C. ν_{max} (liquid film)/ cm^{-1} 3360-3130, 2945-2800, 2224, 1609, 1465-1440. δ_{H} (CDCl_3) 3.41 (dd, $J = 4$ Hz, 1H), 2.69 (br, 2H), 2.09-1.33 (m, 8H). δ_{C} (CDCl_3) 121.91, 75.89, 58.32, 36.40, 31.84, 24.02, 22.45. m/z (CI) 141 ($\text{M}+\text{H}^+$). This was used without purification in the next step.

7,14-diazadispiro[5.1.5.2]pentadecan-1-hydroxy-15-one 7

Sodium (0.33 g, 14.28 mmol) was added slowly to a cooled flask of ethanol (10 mL) under nitrogen and allowed to dissolve fully. The hydroxyaminonitrile **6** (2.0 g, 14.28 mmol) was added to the reaction mixture and allowed to dissolve completely. Cyclohexanone (1.40 g, 1.5 mL, 14.28 mmol) was added to the reaction mixture which was stirred for 3 days.

The reaction mixture was filtered using a sinter funnel and washed with MeCN (100 mL) to give the hydroxy imidazolidinone **7** as an off-white solid (1.70 g, 50% yield), mp 218-219 °C. ν_{max} (KBr)/ cm^{-1} 3300-2920, 1686, 1562. δ_{H} (d-DMSO) 8.39 (br s, 1H), 4.78 (br s, 1H), 1.93-1.26 (m, 19H). δ_{C} (d-DMSO) 176.47, 72.64, 71.44, 62.96, 35.75, 28.94, 24.68, 22.35, 21.15. m/z (CI) 239 (MH^+), 261 ($\text{M}+\text{Na}^+$), 499 ($\text{M})_2\text{Na}^+$. This was used without purification in the next step.

1,4-diazaspiro[4.5]dec-1-en-3-oxo-2-pentanoic acid 1-oxide 13

Sodium tungstate (0.021 g, 0.06 mmol) was added to the hydroxy imidazolidinone **7** (0.30 g, 1.26 mmol) dissolved in acetic acid (6 mL). Hydrogen peroxide solution (30% v/v, 1.5 mL) was added to the reaction mixture which was stirred at rt for 3 days.

The yellow-coloured reaction mixture was concentrated *in vacuo* and redissolved in EtOAc (200 mL), washed with brine solution (50 mL), dried with MgSO₄ and concentrated *in vacuo* to give the spiro pentanoic acid **13** as a yellow solid (0.29 g, 86% yield), mp 139-140 °C (Lit.^[11] 164-166 °C). $\nu_{\max}$ (liquid film)/cm⁻¹ 3200-3000 (br), 2949, 2869, 1728, 1676. δ_{H} (CDCl₃) 9.72 (br, 1H), 9.40 (br, 1H), 2.58-1.24 (m, 18H). δ_{C} (CDCl₃) 178.21, 166.34, 136.55, 88.36, 35.19, 33.63, 24.34, 24.23, 24.01, 22.59, 21.50; m/z (CI) 269 (MH⁺), 291 (M+Na⁺), 559 (M)₂Na⁺. HRMS Observed 269.1497 [M+H]⁺, Calculated 269.1496 [M+H]⁺; Observed 291.1309 [M+Na]⁺, 291.1315 [M+Na]⁺.

Crystal structure determination of **13**

Data collection, structure solution and refinement

A unique X-ray diffraction data set was measured at 295(1) K (Mo-K α radiation, graphite monochromated) for compound **13** on a Rigaku AFC7R four circle diffractometer.^[12]

The structure was solved by the direct methods package SIR92^[13] and refined by full matrix least squares refinement on F^2 using the software packages TeXsan^[14] and WinGX^[15] incorporating SHELXL-2013.^[16] Anisotropic thermal parameters were refined for non-hydrogen atoms; (x, y, z, U_{iso})_H were included and constrained at estimated values. Conventional residuals at convergence are quoted; statistical weights were employed. ORTEP-3^[15] and PLATON^[17] were utilised to prepare material for publication. Full .cif deposition resides with the Cambridge Crystallographic Data Centre (CCDC No 1492181). Copies can be obtained free of charge on application at the following address: <http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi>.

Crystal data

C₁₃H₂₀N₂O₄ $M = 68.31$, monoclinic, space group $P2_1/a$, $a = 21.215(5)$, $b = 10.627(5)$, $c = 6.129(2)$ Å, $\beta = 92.90(2)^\circ$, $V = 1380.0(8)$ Å³, $Z = 4$, $D_c = 1.129$ g cm⁻³, $\mu = 0.0963$

mm⁻¹, Crystal size: 0.30 x 0.20 x 0.20 mm, 3611 reflections collected, 3159 unique ($R_{\text{int}} = 0.021$), $R = 0.052$ [1679 reflections with $I > 2\sigma(I)$], $wR(F^2) = 0.182$ (all data).

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