



Diverse chemical behaviour of 2-hydroxy-functionalized pyrroline-1-oxide

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ABSTRACT

The reactivity of 2-hydroxy-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide was investigated. The title compound showed unexpected reactivity with several different types of reagents.

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Nitrones are frequently used as versatile building blocks in synthetic organic chemistry.¹ Further modification of these compounds before a key synthetic step could be used for the synthesis of complex target molecule by more effective procedures. We recently reported a new method for the preparation of 2-functionalized five-membered cyclic nitrones based on the chemistry of allenes.^{2,3} This work highlights the unexpected impact of 2-hydroxy substitution on the reactivity of the five-membered cyclic nitronone **1**.

Bapat and Durie reported the synthesis of 2-hydroxy-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**1**) via an unusual oxidation of the corresponding pyrroline 1-oxide using a peracid (Scheme 1).⁴

On the other hand, our research group reported an effective alternative synthesis of nitronone **1**, based on cyclization of an allenyl oxime in aqueous solution in the presence of a strong base (Scheme 1).²

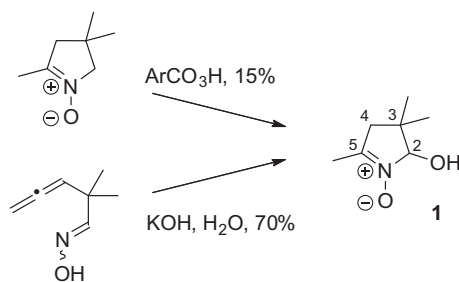
Compound **1** was obtained as a crystalline solid that was stable in air at room temperature and showed some interesting properties and chemical reactivity.

The reaction of **1** with sulfonyl chlorides, to our surprise, did not lead to the expected derivatives substituted at the 2-hydroxy

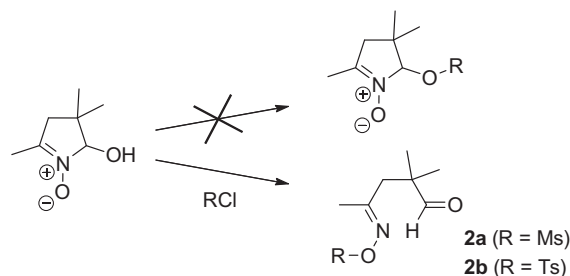
position. Open-chain structures **2** were obtained instead as the exclusive products (Scheme 2). The structures of sulfonates **2** were confirmed by X-ray analysis⁵ of compound **2b** (Fig. 1).

Our previous study showed that nitronone **1** undergoes configurational isomerism at position 2 when dissolved in organic solvents or water. We observed a significant loss of diastereotopism of the methyl groups at position 3 and the hydrogen atoms at position 4, when a CDCl₃ solution of **1** was investigated by NMR experiments at different temperatures (for NMR data of compound **1**, see Supplementary data).²

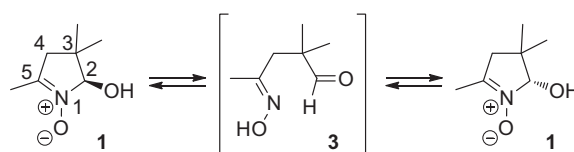
Cleavage of the C–N bond in nitronone **1** under mild reaction conditions (Scheme 2) and the formation of products **2** prompted us to consider aldehyde **3** as an intermediate of nitronone **1** present in solution (Scheme 3).



Scheme 1.



Scheme 2.



Scheme 3.

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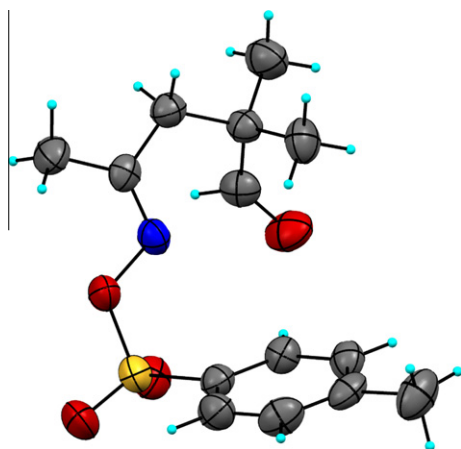
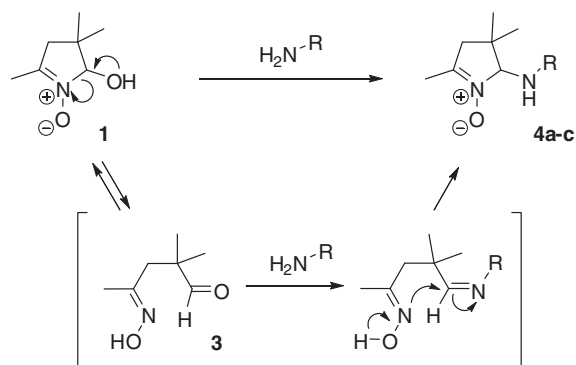


Figure 1. ORTEP representation⁶ of compound **2b**.

Moreover, we have shown that under basic conditions inversion of the stereocentre at position 2 of compound **1** is enhanced. On the other hand, the presence of an acid caused a notable suppression of the above process.² Both observations are in full agreement with the proposed transformation (Scheme 3) as deprotonation of the 2-hydroxy group seems to be necessary for the formation of aldehyde **3**; such a process should be strongly influenced by the acidity/basicity of the solution.



Scheme 4.

The proposed formation of intermediate **3** also readily explains the unusual reactivity of nitronium **1** with primary amines. Treatment of nitronium **1** with various amines at room temperature under solvent-free conditions led to unexpected 2-amino nitrones **4** that might wrongly be considered as products of formal substitution (Scheme 4). Based on the intermediate **3**, a reaction pathway can be proposed. Condensation of the proposed aldehyde **3** with the amine followed by subsequent cyclization of the formed imine gives nitrones **4** (Scheme 4).

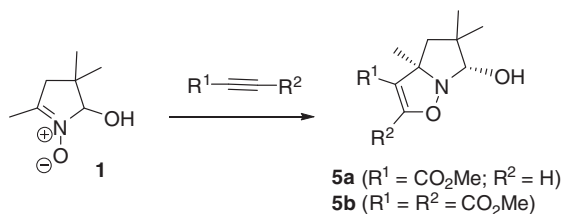
However, in our initial experiments neat reactants in the presence of excess amine had to be mixed, otherwise no reaction would

Table 1
Summary of the reactivity of nitronium **1** under various conditions

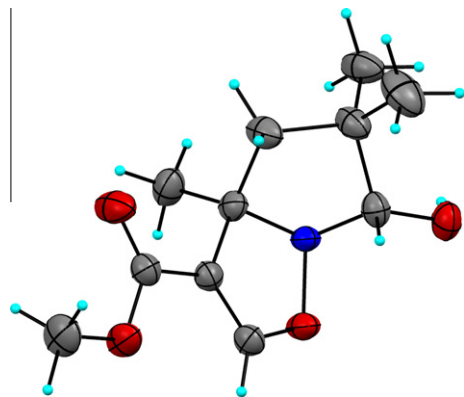
Entry	Substrate	Conditions	Time (h)	Product	Yield
1		CH ₂ Cl ₂ , Et ₃ N, 0 °C to ambient	1		2a (79%)
2		Pyridine 0 °C to ambient	2		2b (64%)
3		Et ₃ N, 4 Å MS, ambient	24		4a (79%)
4		Et ₃ N, 4 Å MS, ambient	24		4b ^b (R = H, 83%) 4c (R = OMe, 76%)
5		Toluene, 60 °C	48		5a (69%)
6		Toluene, ambient	5		5b ^a (76%)

^a For an experimental procedure and spectral data see Ref. 2.

^b For spectral data of the final product see Ref. 2.



Scheme 5.

Figure 2. ORTEP representation⁶ of compound **5a**.

have been observed.² Since the formation of aldehyde **3** is enhanced under basic conditions, we found that the use of triethylamine (as a basic reaction medium) and the presence of 4 Å molecular sieves were suitable conditions (Table 1).

This reaction protocol helped us to solve problems with solvent-free reactions. The presence of air had no effect on the reactions in triethylamine.² Using this new method nitrone **1** was treated with various amines and the results are presented in Table 1, entries 3 and 4. However, the reaction was limited to primary amines and no products were observed on treatment with aromatic amines (tested with aniline) and secondary amines (tested with diethylamine).

Finally, to complete our investigation of the chemical reactivity, reactions of nitrone **1** with several dipolarophiles were performed. Nitrone **1** reacted smoothly with reactive dipolarophiles such as dimethyl acetylene-dicarboxylate and methyl propiolate, to form the corresponding isoxazoles **5a,b** (Scheme 5, Table 1, entries 5 and 6). The products of 1,3-dipolar cycloadditions were obtained as single

diastereomers (**5a,b**)⁷ and single regioisomer (**5a**). The structure of compound **5a** was studied by 2D-NMR experiments (see Supplementary data) and by X-ray analysis⁵ (Fig. 2).

On the other hand, we failed to obtain cycloaddition products with less reactive electron-poor dipolarophiles (e.g., methyl acrylate, maleic anhydride, N-substituted maleimides); similar negative results were obtained with electron-rich dipolarophiles, (allyl alcohol, phenyl-acetylene).

In conclusion, compound **1** has shown unusual chemical reactivity against a broad range of reactants. Reactions with electrophiles (sulfonyl chlorides) gave open-chain aldehydes as the exclusive products that proved the ability of the 2-hydroxy-substituted nitrone to undergo spontaneous C–N bond cleavage in solution. As a consequence, treatment with nucleophiles (primary amines) under basic conditions led to new 2-amino functionalized nitrones. Finally, compound **1** also acted as 1,3-dipole that reacted to give 1,3-dipolar cycloaddition products.

Acknowledgements

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Supplementary data

Supplementary data (containing details of the experimental procedures) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2010.08.103](https://doi.org/10.1016/j.tetlet.2010.08.103).

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5. Crystallographic data for compounds **2b** (CCDC deposition number 767570) and **5a** (CCDC deposition number 767571) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
6. Carbon (grey), oxygen (red), nitrogen (blue) and sulfur (yellow) atoms are drawn as principal ellipses (70% probability level); hydrogen atoms are drawn as fixed-size spheres (cyan).
7. Based on an NMR study of crude reaction mixtures.