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One-pot, three-component synthesis of five-membered cyclic nitrones by addition/cyclization/condensation domino reaction

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ABSTRACT

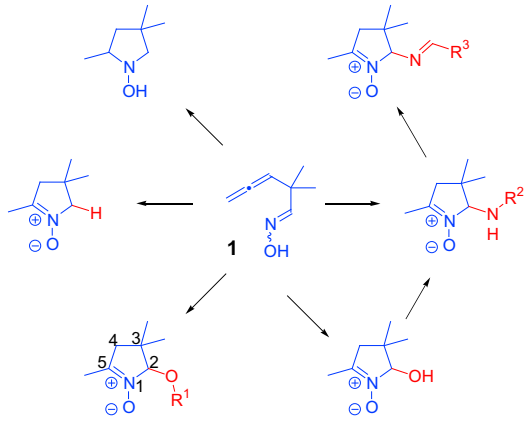
A new approach to five-membered cyclic nitrones connected with the incorporation of a planar aromatic ring system into the structure is described. This procedure is based on an allenyloxime one-pot domino transformation under simple base catalysis in alcoholic and aqueous solvents. The structure of obtained nitrones was studied by X-ray analysis and the reactivity of products in 1,3-dipolar cycloadditions was tested.

1. Introduction

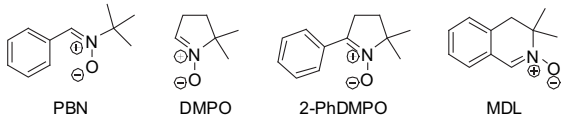
The consistent interest of our research group in allene chemistry has been recently documented by a published results.[1,2] We described the ability of 2,2-dimethylpenta-3,4-dienal oxime **1** to undergo heterocyclizations under various conditions leading to stable functionalized five-membered cyclic nitrones (Scheme 1). These presented methods provide easy access to completely new nitrone-type building blocks. In most cases, each process involves only one reaction step, where cyclization together with introduction of a functional group takes place.[2]

Nitrones enjoy great popularity among chemists due to their numerous applications as building blocks in organic synthesis[3] or as spin traps.[4] Furthermore, in the last decade they have shown widespread biological activities (e.g., antitumour, neuroprotective, *anti*-stroke, suppression of age-associated degeneration), even though they possess simple structure (Scheme 2) and the structure–activity relationship has not been determined.[5,7]

Interestingly, syntheses of planar aromatic ring systems containing polar side functionalities and in particular, the incorporation of fused polyaromatic rings into the structure of



Scheme 1.



Scheme 2. Examples of biologically active nitrones.

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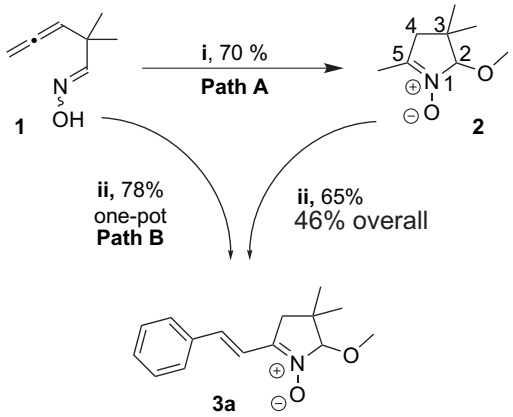
nitrones was found to be useful in the design of new antitumour DNA intercalating agents.[6]

With this background in mind, combined with the actual application of nitrones as therapeutics,[7] we want to report a new one-pot transformation of allenyloxime **1**. The 5-methyl substitution is present in the structure of all our previously reported cyclic nitrones (see Scheme 1). This paper applies the reactivity of the 5-methyl group for the incorporation of planar aromatic system at the nitrone structure.

2. Results and discussion

Methyl groups located at nitrone C=N$^+$ carbon atom are well-known to undergo deprotonation in the presence of a strong base and then to react with electrophiles.[8] To test the reactivity of structurally different substrates, we chose nitrone **2** for initial experiments. As we had shown earlier, nitrone **2** is available from oxime **1** via a base catalyzed cyclization in methanol (**1**→**2**, Scheme 3).[2]

According with the previously published procedures,[9] we have successfully performed the condensation of nitrone **2** in methanolic solution in the presence of potassium hydroxide (4 equiv) and benzaldehyde (**2**→**3a**, Scheme 3). The reaction offered aryl-modified cyclic nitrone **3a** in 46% overall yield (path A).

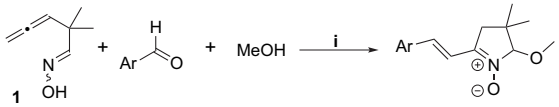


Scheme 3. Preparation of nitrone **3a**: (i) KOH (0.1 equiv), Δ, 4 h, 70%; (ii) KOH (4 equiv), benzaldehyde, MeOH, Δ. Path A overall time 8 h, overall yield 46%; Path B 4 h, yield 78%.

Because the reaction conditions for both the reaction steps (i, ii) are similar, we have subsequently exercised one-pot modification for this reaction transformation. Simple mixing of allenyloxime **1**, potassium hydroxide and benzaldehyde in boiling methanol led to desired product in this effective manner and high yield (**1**→**3a**, Scheme 3, path B).

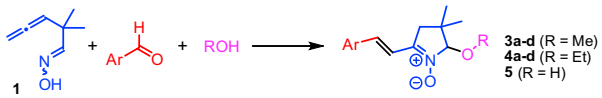
At first, we tried to explore limitations of this reaction protocol in respect to an aldehyde component in the reaction mixture. Increasing sterical demands of fused aromatic aldehydes, i.e., switching from benzaldehyde to anthracene carbaldehyde or phenanthrene carbaldehyde, does not lead to significant decrease in yields under identical reaction conditions. Isolated yields of corresponding nitrones were found within 10% interval (Scheme 4; Table 1, entries 1–4).

The structure of selected nitrone **3c** was studied by X-ray analysis[15] that fully confirmed the expected structure (Fig. 1).



Scheme 4. One-pot domino reaction of allenyloxime **1** in methanol: (i) KOH (4 equiv), Δ, aromatic aldehyde.

Table 1
Summary of one-pot synthesis of nitrones **3**–**5** from **1**



Entry	Ar	Solvent (ROH)	Temp.	Reaction time (h)	Nitrone	Yield (%)
1	Phenyl	MeOH	Reflux	3	**3a**	78
2	1-Naphthyl	MeOH	Reflux	3	**3b**	73
3	9-Anthryl	MeOH	Reflux	3	**3c**	66
4	9-Phenanthryl	MeOH	Reflux	3	**3d**	72
5	Phenyl	EtOH	Reflux/ambident	8.5	**4a**	51
6	1-Naphthyl	EtOH	Reflux/ambident	8.5	**4b**	50
7	9-Anthryl	EtOH	Reflux/ambident	8.5	**4c**	54
8	9-Phenanthryl	EtOH	Reflux/ambident	8.5	**4d**	50
9	Phenyl	Water	70 °C	24	**5**	29

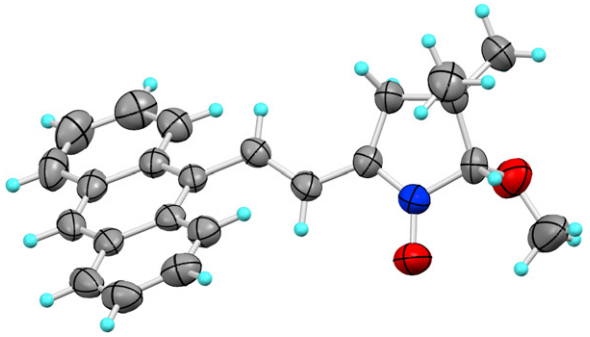
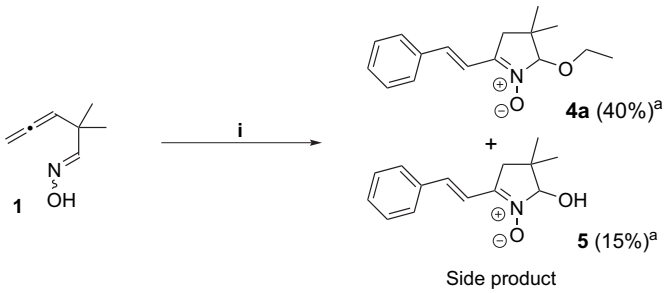


Figure 1. ORTEP representation[14] of compound **3c**.

Additionally, we found that this procedure is limited to non-enolizable aldehydes. All attempts to incorporate aldehydes bearing α-hydrogens into the structure of final product, even under milder conditions (lower temperature) failed.

Interestingly, a simple exchange of methanol for a higher alcoholic solvent under analogous conditions, does not lead exclusively to expected 2-alkoxy substituted products. Thus, a 2-hydroxy substituted product was observed as a detectable product of a side process in the reaction where methanol was replaced by ethanol. The isolated nitrone **5** in 15% yield illustrates situation (Scheme 5, Fig. 2).[15] Moreover, secondary and tertiary alcohols were found not to be reactive to yield single products (only complex reaction mixtures were obtained).



Scheme 5. One-pot domino reaction of allenyloxime **1** in ethanol: (i) KOH (4 equiv), EtOH, Δ, benzaldehyde; [a]isolated yields.[10]

To explain the formation of compound **5**, the formulation of a new reaction pathway is necessary (Scheme 6). In previous work we established that reaction starts by a nucleophilic attack of the alkoxide anion at the carbon atom of the C=N bond of allenyloxime **1**. The attack is followed by a cyclization in the second step, resulting in alkoxy-substituted nitrone.[2] A further step then