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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

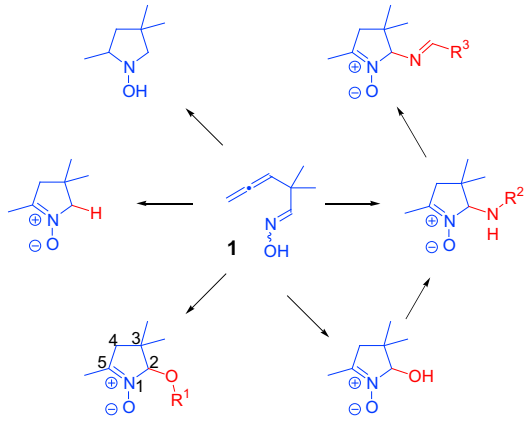
A new approach to five-membered cyclic nitrones connected with the incorporation of a planar aromatic ring system into the structure is described. This procedure is based on an allenyloxime one-pot domino transformation under simple base catalysis in alcoholic and aqueous solvents. The structure of obtained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

1. Introduction

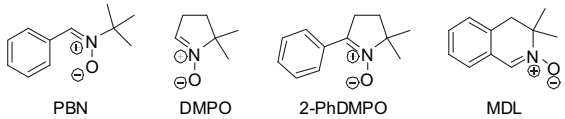
The consistent interest of our research group in allene chemistry has been recently documented by a published results.[1,2] We described the ability of 2,2-dimethylpenta-3,4-dienal oxime **1** to undergo heterocyclizations under various conditions leading to stable functionalized five-membered cyclic 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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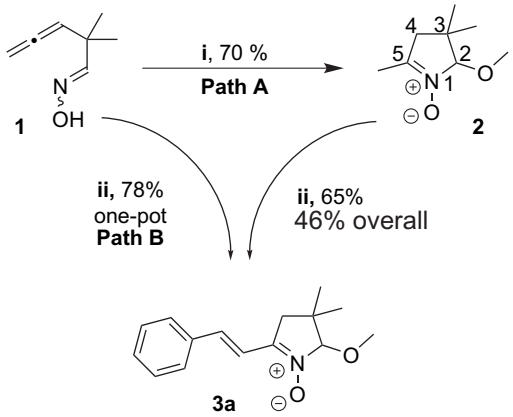
nitrones was found to be useful in the design of new antitumour DNA intercalating agents.[6]

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).

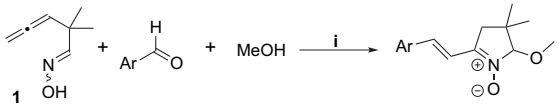


Scheme 3. Preparation of nitrone **3a**: (i) KOH (0.1 equiv), Δ, 4 h, 70%; (ii) KOH (4 equiv), benzaldehyde, MeOH, Δ. Path A overall time 8 h, overall yield 46%; Path B 4 h, yield 78%.

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).

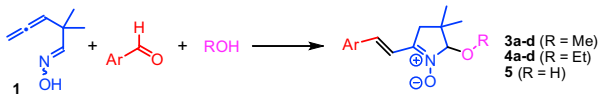
At first, we tried to explore limitations of this reaction protocol in respect to an aldehyde component in the reaction mixture. Increasing sterical demands of fused aromatic aldehydes, i.e., switching from benzaldehyde to anthracene carbaldehyde or phenanthrene carbaldehyde, does not lead to significant 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

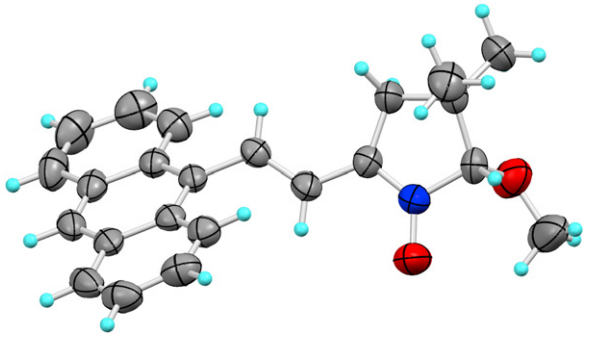
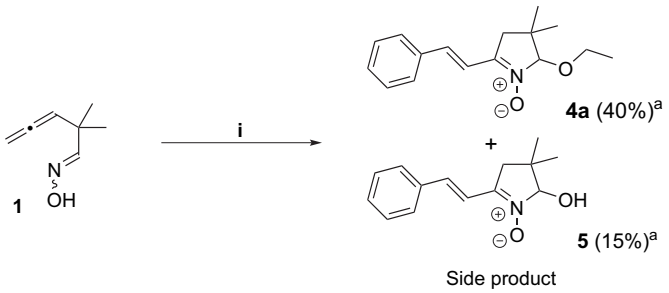


Figure 1. ORTEP representation[14] of compound **3c**.

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

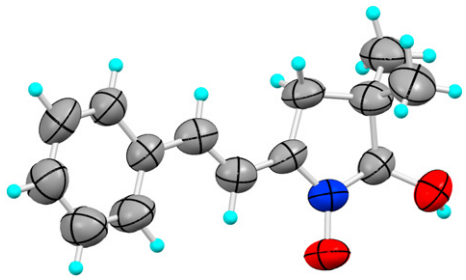
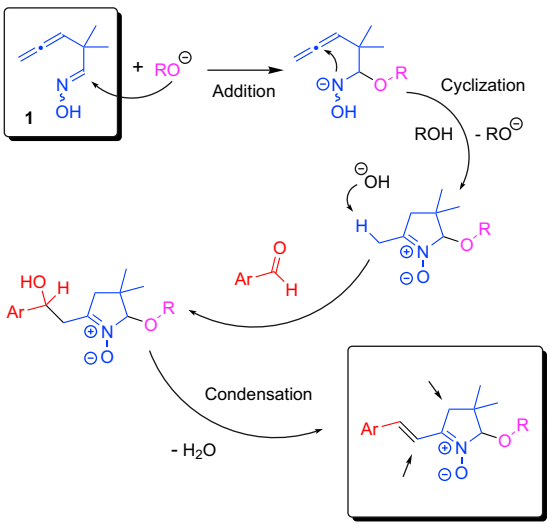


Figure 2. Ortep representation[14] of compound **5**.



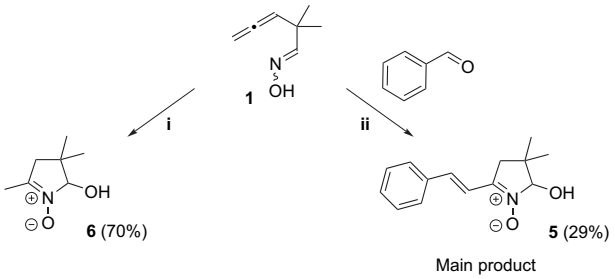
Scheme 6. Domino reaction pathway of allenyloxime **1**; arrows at the structure of the final product show positions where in this reaction carried out in CD_3OD (instead of methanol) incorporation of deuterium was observed.

involves 5-methyl deprotonation with participation of the base present and consequent condensation with aldehyde with formation of the dehydrated final product.

It should be noted that during cyclization step, protonation of former allenyloxime at positions 3 and 5 is possible. Although one could think about more straight process connected with a direct attack of the intermediate formed by the nucleophilic attack of alkoxide anion at the present aldehyde. But such a mechanism may be excluded, according with results obtained in the case of the reaction in CD_3OD. Besides expected CD_3O group instead CH_3O in position 2 and deuterium at position 4, the final reaction product showed incorporation of deuterium at carbon atom of the C=C double bond (shown in Scheme 6). This way the participation of the solvent in the reaction pathway was clearly documented.

It is obvious, that first addition reaction step determines the type of substitution in position 2 of the final nitrone. Accordingly, compound **5** must result from hydroxide attack rather than alkoxide anion attack at the beginning of the reaction cascade. We have already shown that the addition of the hydroxide anion can be effectively used for the preparation of 2-hydroxy nitrones (shown as the left part of Scheme 7).[2] When analogous conditions[11] were tested in the presence of benzaldehyde, nitrone **5** was isolated in low yield as the main product (Scheme 7).

This supports the fact that the formation of side product **5**, in the previously shown procedure (Scheme 5), is probably affected by a high concentration of hydroxide promoter (4 equiv). Under such conditions, we can assume that in ethanol, the elevated hydroxide concentration initiates a competitive reaction. The reason for this



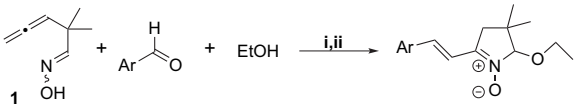
Scheme 7. Transformation of oxime **1** in aqueous solutions: (i) KOH (4 equiv), H_2O, 70 °C; (ii) KOH (4 equiv), H_2O, 60 °C.

observation is probably due to the increased sterical demand of the nucleophile (ethoxide anion), since no desired products with alkoxy substitution in position 2 were observed with better nucleophiles (reactions with secondary and tertiary alcohols). Furthermore, methanol is more acidic than ethanol and therefore formation of the reagent (ethoxide) will also be harder. On the other hand, cyclization under same conditions in methanol leads exclusively to desired nitrone with no detectable formation of the side product **5**.

Therefore to eliminate the side reaction pathway in ethanol, we had to decrease the concentration of base to a catalytic amount (0.1 equiv). However, more than one equivalent of base was necessary for the condensation reaction step, where four equivalents of potassium hydroxide in methanol were found to be the most efficient choice.

For that reason in the case of reaction in ethanol we have to divide the reaction procedure into two steps: (i) allenyloxime cyclization at reflux in the presence of catalytic amount of base (formation of 2-alkoxy-substituted nitrone), (ii) subsequent condensation with aldehydes at elevated concentration of base at room temperature.

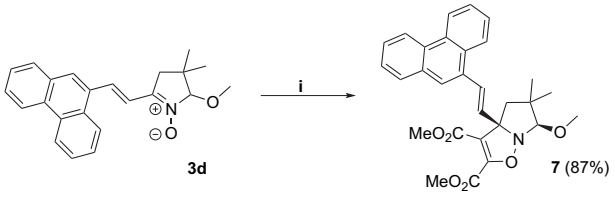
Both procedure parts were again arranged as one-pot modification. This reaction set-up leads exclusively to nitrones **4a–d** together with no detectable hydroxy-substituted products (Scheme 8, Table 1, entries 5–8).



Ar = Phenyl (**a**), 1-Naphthyl (**b**), 9-Anthryl (**c**), 9-Phenanthryl (**d**) **4a-d** (50-54%)

Scheme 8. One-pot two-step transformation of allenyloxime **1** in ethanol: (i) KOH (0.1 equiv), Δ; (ii) KOH (3.9 equiv), aromatic aldehyde, room temperature.

Ability of prepared nitrones to undergo 1,3-dipolar cycloaddtions and form corresponding isoxazoles was tested on selected nitrone **3d** with dimethyl acetylenedicarboxylate as a reactive dipolarophile. Expected compound **7** was isolated in high yield (Scheme 9).



Scheme 9. 1,3-Dipolar cycloaddition of nitrone **3d**: (i) dimethyl acetylenedicarboxylate, toluene, Δ.

Compound **7** was found as a single diastereomer (racemate).[12] The relative stereochemistry was confirmed by X-ray analysis[15] (Fig. 3). Similar diastereoselectivity for 1,3-dipolar cycloaddition was observed for nitrone **2** and its structural analogs.[2]

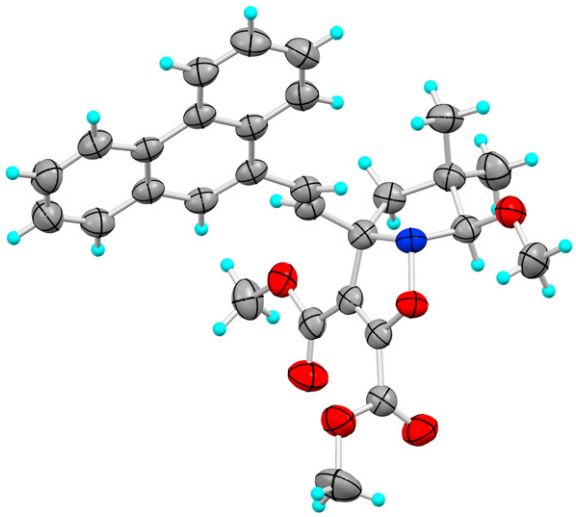


Figure 3. ORTEP representation[14] of compound **7**.

3. Conclusion

A new approach to functionalized five-membered cyclic nitrones bearing diverse-size fused polyaromatic structural motifs is presented. The developed method is based on a one-pot reaction of allenyloxime under mild, base catalyzed conditions. The reaction mixtures consist of three components: 2,2-dimethyl-3,4-dienal oxime, aromatic aldehyde and alcohol (or water) serving as the reagent/solvent. Nine selected derivatives of target nitrones were prepared to explore and indicate the possible limitations of the presented method (Table 1). The reaction in methanol offers high yields and fulfils the definition of domino arrangement.[16]

4. Experimental section

4.1. Instrumentation and materials

All chemicals were used as purchased. For preparation of compounds **1**, **2** see Ref. 2. Solvents (methanol, ethanol) were fractionally distilled before use. Toluene was dried over sodium and stored over molecular sieves. Column chromatography was performed on Horizon HPFC system (Biotage), with FLASH Si 25+M cartridge. Melting points are uncorrected. FTIR spectra were recorded on a Genesis ATI (Unicam) apparatus. NMR spectra were collected on a Bruker Avance 300 spectrometer. TMS (δ=0.00 ppm) or $CHCl_3$ (δ=7.27 ppm) for ^1H and $CDCl_3$ (77.23 ppm) for ^{13}C NMR were used as internal standards, interaction constants are in Hertz. MS data were obtained with MS TRIO 1000 (Fisons) apparatus at 70 eV in the electron impact mode, HRMS with Waters-Micromas Q-TOF (ESSI positive mode). Diffraction data were collected on a Kuma KM-4 four-circle CCD diffractometer and corrected for Lorentz and polarization effects. The structures were solved by direct methods and refined using the **SHELXTL** program package.[13] The hydrogen atoms were placed in calculated idealized positions and refined as riding.

4.2. General procedure for nitrones 3a–d preparation

Potassium hydroxide (269 mg, 4.79 mmol,) was dissolved in methanol (5 mL), then allenyloxime **1** (150 mg, 1.20 mmol) and aromatic aldehyde (1.32 mmol) were added. The mixture was heated at reflux for 3 h. The solution was concentrated under reduced pressure; water (3 mL) was added and mixture was extracted to dichloromethane (8×5 mL). Combined extracts were dried over $MgSO_4$ and the solvent evaporated. The residual oil was purified by column chromatography (Et_2O/EtOAc), and the residual content of solvent was evaporated under high vacuum (10^{-2} mbar).

*4.2.1. (E)-2-Methoxy-3,3-dimethyl-5-(2-phenylethenyl)-3,4-dihydro-2H-pyrrole 1-oxide (**3a**).* Crude product was sonificated in hexane until a slightly yellow precipitate was formed. The suspension was then cooled to −15 °C for 30 min. Formed solid was separated by filtration, washed with hexane and dried under vacuum to give **3a** as white solid (229 mg, 78%), mp 109–110 °C. δ_H ($CDCl_3$): 1.15 (s, 3H, C–CH_3), 1.22 (s, 3H, C–CH_3), 2.55 (d, $^2J_{H,H}$ 16.3, 1H, CH_2), 2.73 (d, $^2J_{H,H}$ 16.3, 1H, CH_2), 3.87 (s, 3H, O–CH_3), 4.52 (s, 1H, CH–O), 6.91 (d, $^3J_{H,H}$ 16.5, 1H, C_{Ar}–CH=C*H*), 7.28–7.55 (m, 6H, C_{Ar}–C*H*=CH+CH_{Ar}); δ_C ($CDCl_3$): 22.0 (C–*C*H_3), 27.3 (C–*C*H_3), 37.1 (*C*–CH_3), 41.0 (CH_2), 61.0 (O–CH_3), 108.2 (CH–O), 116.2 (CH), 127.5 (CH), 129.0 (CH), 129.3 (CH), 136.2 (C_{Ar}), 136.9 (CH), 142.9 (C=N); IR (KBr): 694, 754, 962, 1117, 1142, 1196, 1215, 1275, 1541, 2870, 2953, 2970, 3035; MS *m*/*z* (%): 245 (M^+, 20), 215 (25), 198 (100), 128 (60), 115 (20), 77 (35), 71 (50). Calcd for $C_{15}H_{20}NO_2$ (MH^+) 246.1494, HRMS found 246.1492.

*4.2.2. (E)-2-Methoxy-3,3-dimethyl-5-(2-naphthalene-1-ylethenyl)-3,4-dihydro-2H-pyrrole 1-oxide (**3b**).* Et_2O/EtOAc=3:1, R_f 0.17, yellow solid (258 mg, 73%), mp 121–123 °C. δ_H ($CDCl_3$): 1.18 (s, 3H, C–CH_3), 1.25 (s, 3H, C–CH_3), 2.65 (d, $^2J_{H,H}$ 16.3, 1H, CH_2), 2.84 (d, $^2J_{H,H}$ 16.3, 1H, CH_2), 3.89 (s, 3H, O–CH_3), 4.55 (s, 1H, CH–O), 7.43–7.56 (m, 4H), 7.77–7.88 (m, 4H), 8.12 (d, $J_{H,H}$ 7.9, 1H); δ_C ($CDCl_3$): 21.9 (C–*C*H_3), 27.2 (C–*C*H_3), 37.0 (*C*–CH_3), 41.1 (CH_2), 61.0 (O–CH_3), 108.1 (CH–O), 118.3 (CH), 123.0 (CH), 124.4 (CH), 125.7 (CH), 126.0 (CH), 126.5 (CH), 128.8 (CH), 129.6 (CH), 131.1 (C_{Ar}), 133.1 (CH), 133.8 (C_{Ar}), 142.6 (C=N); IR (KBr): 777, 798, 966, 1117, 1138, 1200, 1261, 1288, 1362, 1404, 1533, 2872, 2927, 2958, 3045; MS *m*/*z* (%): 295 (M^+, 100), 248 (75), 178 (100), 165 (30), 152 (90), 86 (30), 71 (65), 41 (45). Calcd for $C_{19}H_{22}NO_2$ (MH^+) 296.1651, HRMS found 296.1648.

*4.2.3. (E)-5-(2-Anthracene-9-ylethenyl)-2-methoxy-3,3-dimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**3c**).* Et_2O, R_f 0.17, yellow solid (275 mg, 66%), mp 148–150 °C. δ_H ($CDCl_3$): 1.23 (s, 3H, C–CH_3), 1.33 (s, 3H, C–CH_3), 2.94 (d, $^2J_{H,H}$ 16.4, 1H, CH_2), 2.77 (d, $^2J_{H,H}$ 16.4, 1H, CH_2), 3.93 (s, 3H, O–CH_3), 4.62 (s, 1H, CH–O), 7.30 (d,, $^3J_{H,H}$ 16.8, 1H, C_{Ar}–CH=C*H*), 7.33–7.52 (m, 4H, CH_{Ar}), 7.91–8.01 (m, 3H, C_{Ar}–*C*H=CH+*C*H_{Ar}), 8.25–8.28 (m, 2H, CH_{Ar}), 8.40 (s, 1H, CH_{Ar}); δ_C ($CDCl_3$): 22.3 (C–*C*H_3), 27.5 (C–*C*H_3), 37.3 (*C*–CH_3), 41.4 (CH_2), 61.4 (O–CH_3), 108.5 (CH–O), 124.8 (CH), 125.5 (CH), 125.6 (CH), 126.3 (CH), 128.0 (CH), 129.0 (CH), 129.6 (C_{Ar}), 131.0 (C_{Ar}), 131.6 (C_{Ar}), 133.6 (CH), 142.1 (C=N); IR (KBr): 733, 906, 987, 1109, 1188, 1205, 1269, 1286, 1400, 1462, 1535, 2816, 2854, 2868, 2910, 2927, 2958, 2985, 3045; MS *m*/*z* (%): 345 (M^+, 100), 328 (40), 298 (90), 228 (90), 215 (40), 202 (100), 126 (30), 86 (40), 71 (60), 41 (50). Calcd for $C_{23}H_{24}NO_2$ (MH^+) 346.1807, HRMS found 346.1805. Compound was subjected to X-ray diffraction.

*4.2.4. (E)-2-Methoxy-3,3-dimethyl-5-(2-phenanthrene-9-ylethenyl)-3,4-dihydro-2H-pyrrole 1-oxide (**3d**).* Et_2O/EtOAc=2:1, R_f 0.13, yellow solid (300 mg, 72%), mp 170–172 °C. δ_H ($CDCl_3$): 1.20 (s, 3H, C–CH_3), 1.28 (s, 3H, C–CH_3), 2.69 (d, $^2J_{H,H}$ 16.3, 1H, CH_2), 2.87 (d, $^2J_{H,H}$ 16.3, 1H, CH_2), 3.91 (s, 3H, O–CH_3), 4.58 (s, 1H, CH–O), 7.53–7.92 (m, 7H), 8.13–8.17 (m, 2H), 8.63–8.74 (m, 2H); δ_C ($CDCl_3$): 22.1 (C–*C*H_3), 27.4 (C–*C*H_3), 37.3 (*C*–CH_3), 41.3 (CH_2), 61.1 (O–CH_3), 108.4 (CH–O), 118.9 (CH), 122.7 (CH), 123.4 (CH), 124.0 (CH), 126.0 (CH), 126.9 (CH), 127.0 (CH), 127.2 (CH), 127.5 (CH), 129.3 (CH), 130.2 (C_{Ar}), 130.7 (C_{Ar}), 130.9 (C_{Ar}), 131.6 (C_{Ar}), 132.1 (C_{Ar}), 133.8 (CH), 142.8 (C=N); IR (KBr): 723, 739, 984, 1001, 1115, 1144, 1196, 1271, 1286, 1367, 1404, 1537, 2866, 2926, 2954, 3016, 3047; MS *m*/*z* (%): 345 (M^+, 25), 328

(35), 298 (30), 228 (100), 215 (25), 202 (40), 126 (30), 85 (20), 71 (20). Calcd for $C_{23}H_{24}NO_2$ (MH^+) 346.1807, HRMS found 346.1807.

4.3. General procedure for nitrones 4a–d preparation

Potassium hydroxide (7 mg, 0.12 mmol) was dissolved in methanol (5 mL), then allenyloxime **1** (150 mg, 1.20 mmol) was added. Mixture was heated at reflux for 5.5 h. The solution was cooled down to room temperature, then potassium hydroxide (262 mg, 4.67 mmol) was dissolved and aromatic aldehyde (1.32 mmol) was added. The mixture was stirred at room temperature for 3 h and then was concentrated under reduced pressure; water (3 mL) was added and mixture was extracted to dichloromethane (8×5 mL). The combined extracts were dried over $MgSO_4$ and solvents evaporated. Residual oil was purified by column chromatography (Et_2O/EtOAc). Solid products were obtained by evaporation of residual content of solvent under high vacuum (10^{-1} mbar), if necessary crystallization was supported by refrigerating overnight.

*4.3.1. (E)-2-Ethoxy-3,3-dimethyl-5-(2-phenylethenyl)-3,4-dihydro-2H-pyrrole 1-oxide (**4a**).* Et_2O/EtOAc=7:2, R_f 0.21, yellow solid (159 mg, 51%), mp 74–76 °C. δ_H ($CDCl_3$): 1.15 (s, 3H, C–CH_3), 1.21 (s, 3H, C–CH_3), 1.26 (t, $^3J_{H,H}$ 7.0, 3H, CH_2–CH_3), 2.54 (d, $^2J_{H,H}$ 16.3, 1H, N=C–CH_2), 2.74 (d, $^2J_{H,H}$ 16.3, 1H, N=C–CH_2), 3.85–3.95 (m, 1H, O–CH_2), 4.33–4.44 (m, 1H, O–CH_2), 4.61 (s, 1H, CH–O), 6.90 (d, $^3J_{H,H}$ 16.5, 1H, C_{Ar}–CH=C*H*), 7.29–7.53 (m, 6H, C_{Ar}–*C*H=CH+*C*H$_{Ar}$); δ_C ($CDCl_3$): 15.4 (CH_2–CH_3) 22.2 (C–CH_3), 27.3 (C–CH_3), 37.0 (*C*–CH_3), 41.0 (N=C–CH_2), 69.0 (O–CH_2), 106.9 (CH–O), 116.3 (CH), 127.5 (CH), 129.0 (CH), 129.3 (CH), 136.3 (C_{Ar}), 136.8 (CH), 142.7 (C=N); IR (KBr): 688, 754, 958, 1041, 1105, 1149, 1176, 1194, 1227, 1271, 1292, 1371, 1541, 2868, 2904, 2941, 2958, 2980, 3022, 3037, 3057; MS *m*/*z* (%): 260 (M^+, 75), 215 (50), 198 (100), 128 (50), 91 (25), 77 (35), 57 (50), 41 (60). Calcd for $C_{16}H_{22}NO_2$ (MH^+) 260.1651, HRMS found 260.1654.

*4.3.2. (E)-2-Ethoxy-3,3-dimethyl-5-(2-naphthalene-1-ylethenyl)-3,4-dihydro-2H-pyrrole 1-oxide (**4b**).* Et_2O/EtOAc=5:1, R_f 0.18, yellow oil (185 mg, 50%). δ_H ($CDCl_3$): 1.17 (s, 3H, C–CH_3), 1.23 (s, 3H, C–CH_3), 1.26 (t, $^3J_{H,H}$ 7.1, 3H, CH_2–CH_3), 2.64 (d, $^2J_{H,H}$ 16.3, 1H, N=C–CH_2), 2.83 (d, $^2J_{H,H}$ 16.3, 1H, N=C–CH_2), 3.84–3.95 (m, 1H, O–CH_2), 4.35–4.50 (m, 1H, O–CH_2), 4.63 (s, 1H, CH–O), 7.25–7.52 (m, 4H), 7.74–7.87 (m, 4H), 8.11–8.14 (m, 1H); δ_C ($CDCl_3$): 15.4 (CH_2–CH_3) 22.2 (C–CH_3), 27.4 (C–CH_3), 37.1 (*C*–CH_3), 41.2 (N=C–CH_2), 69.0 (O–CH_2), 106.9 (CH–O), 118.5 (CH), 123.2 (CH), 124.6 (CH), 125.9 (CH), 126.1 (CH), 126.6 (CH), 129.0 (CH), 129.7 (CH), 131.3 (C_{Ar}), 133.1 (CH), 133.2 (C_{Ar}), 133.9 (C_{Ar}), 142.8 (C=N); IR (film): 658, 702, 775, 796, 966, 1036, 1107, 1180, 1198, 1217, 1261, 1284, 1346, 1371, 1404, 1443, 1468, 1537, 1633, 2870, 2931, 2970, 3057; MS *m*/*z* (%): 309 (M^+, 20), 265 (25), 248 (100), 231 (25), 178 (80), 152 (20). Calcd for $C_{20}H_{24}NO_2$ (MH^+) 310.1807, HRMS found 310.1806.

*4.3.3. (E)-5-(2-Anthracene-9-ylethenyl)-2-ethoxy-3,3-dimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**4c**).* Et_2O, R_f 0.29, yellow solid (233 mg, 54%), mp 156–158 °C. δ_H ($CDCl_3$): 1.25 (s, 3H, C–CH_3), 1.30 (t, $^3J_{H,H}$ 7.1, 3H, CH_2–CH_3), 1.33 (s, 3H, C–CH_3), 2.78 (d, $^2J_{H,H}$ 16.4, 1H, N=C–CH_2), 2.96 (d, $^2J_{H,H}$ 16.4, 1H, N=C–CH_2), 3.89–4.00 (m, 1H, O–CH_2), 4.40–4.50 (m, 1H, O–CH_2), 4.72 (s, 1H, CH–O), 7.30 (d, $^3J_{H,H}$ 16.8, 1H, C_{Ar}–CH=C*H*), 7.45–7.51 (m, 4H, CH_{Ar}), 7.92–8.02 (m, 3H, C_{Ar}–*C*H=CH+*C*H$_{Ar}$), 8.26–8.29 (m, 2H, CH_{Ar}), 8.41 (s, 1H, CH_{Ar}); δ_C ($CDCl_3$): 15.5 (CH_2–CH_3) 22.4 (C–CH_3), 27.5 (C–CH_3), 37.2 (*C*–CH_3), 41.3 (N=C–CH_2), 69.3 (O–CH_2), 107.0 (CH–O), 125.0 (CH), 125.5 (CH), 125.6 (CH), 126.3 (CH), 128.0 (CH), 129.0 (CH), 129.6 (C_{Ar}), 131.0 (C_{Ar}), 131.6 (C_{Ar}), 133.4 (CH), 141.9 (C=N); IR (KBr): 735, 912, 989, 1084, 1099, 1171, 1184, 1205, 1269, 1282, 1537, 1620, 2868, 2899, 2927, 2956, 3043; MS *m*/*z* (%): 359 (M^+, 80), 298 (100), 228 (50), 202 (30), 71 (20), 43 (30). Calcd for $C_{24}H_{26}NO_2$ (MH^+) 360.1964, HRMS found 360.1960.

*4.3.4. (E)-2-Ethoxy-3,3-dimethyl-5-(2-phenanthrene-9-ylethenyl)-3,4-dihydro-2H-pyrrole 1-oxide (**4d**).* $Et_2O \rightarrow Et_2O$/EtOAc=1:2, R_f 0.14 (Et_2O), yellow oil (215 mg, 50%). δ_H ($CDCl_3$): 1.21 (s, 3H, C–CH_3), 1.27 (s, 3H, C–CH_3), 1.29 (t, $^3J_{H,H}$ 7.0, 3H, CH_2–CH_3), 2.69 (d, $^2J_{H,H}$ 16.3, 1H, N=C–CH_2), 2.89 (d, $^2J_{H,H}$ 16.3, 1H, N=C–CH_2), 3.89–4.00 (m, 1H, O–CH_2), 4.38–4.48 (m, 1H, O–CH_2), 4.67 (s, 1H, CH–O), 7.53–7.92 (m, 7H), 8.13–8.18 (m, 2H), 8.63–8.75 (m, 2H); δ_C ($CDCl_3$): 15.5 (CH_2–CH_3) 22.3 (C–CH_3), 27.4 (C–CH_3), 37.2 (*C*–CH_3), 41.3 (N=C–CH_2), 69.1 (O–CH_2), 107.0 (CH–O), 119.1 (CH), 122.7 (CH), 123.5 (CH), 124.1 (CH), 126.1 (CH), 126.9 (CH), 127.0 (CH), 127.2 (CH), 127.5 (CH), 129.4 (CH), 130.3 (C_{Ar}), 130.7 (C_{Ar}), 130.9 (C_{Ar}), 131.7 (C_{Ar}), 132.2 (C_{Ar}), 133.7 (CH), 142.7 (C=N); IR (film): 723, 748, 964, 1105, 1130, 1180, 1198, 1269, 1402, 1533, 2846, 2866, 2906, 2926, 2968, 3062; MS *m*/*z* (%): 359 (M^+, 30), 298 (100), 281 (30), 228 (80), 202 (45). Calcd for $C_{24}H_{26}NO_2$ (MH^+) 360.1964, HRMS found 360.1958.

4.4. (*E*)-2-Hydroxy-3,3-dimethyl-5-(2-phenylethenyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (5)

Potassium hydroxide (269 mg, 4.79 mmol) was dissolved in water (10 mL), then allenyloxime **1** (150 mg, 1.20 mmol) and benzaldehyde (140 mg, 1.32 mmol) was added. The mixture was heated to 60 °C (temperature of oil bath) for 24 h. Afterwards, the solution was saturated by addition of NaCl (2 g) and extracted to dichloromethane (5×10 mL). The combined extracts were dried over $MgSO_4$ and evaporated. The residual oil was purified by column chromatography (EtOAc, R_f 0.40) to give white solid (81 mg, 29%), mp 177–179 °C. δ_H ($CDCl_3$): 1.18 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.59 (d, $^2J_{H,H}$ 16.2, 1H, CH_2), 2.76 (d, $^2J_{H,H}$ 16.5, 1H, CH_2), 5.19 (s, 1H, N–CH), 6.94 (d, $^3J_{H,H}$ 16.5, 1H, C_{Ar}–CH=C*H*), 7.34–7.55 (m, 6H, C_{Ar}–*C*H=CH+*C*H$_{Ar}$), 8.49 (s, 1H, OH); δ_C ($CDCl_3$): 22.1 (CH_3), 26.8 (CH_3), 37.3 (*C*–CH_3), 40.6 (CH_2), 99.8 (CH–O), 116.0 (CH), 127.7 (CH), 129.0 (CH), 129.6 (CH), 135.8 (C_{Ar}), 138.6 (CH), 143.4 (C=N); IR (KBr): 754, 976, 1163, 1219, 1277, 1396, 1556, 1616, 2744, 2872, 2927, 2964, 3046; MS *m*/*z* (%): 231 (M^+, 10), 128 (100), 115 (30), 91 (30), 77 (70), 57 (50), 51 (30). Calcd for $C_{14}H_{18}NO_2$ (MH^+) 232.1338, HRMS found 232.1334. Compound was subjected to X-ray diffraction.

4.5. (*E*)-Dimethyl 6-methoxy-5,5-dimethyl-3a-(2-phenanthrene-9-ylethenyl)-3a,4,5,6-tetrahydropyrrolo [1,2-*b*]isoxazole-2,3-dicarboxylate (7)

Nitrone **3d** (80 mg, 0.232 mmol) was dissolved in dry toluene (4 mL) and dimethyl acetylenedicarboxylate (46 mg, 3.24 mmol) was added. The mixture was heated at reflux for 30 min. The solvent was evaporated and the residual oil was dissolved in methanol (2 mL). The solution was cooled to −15 °C and sonificated until a precipitate was formed. The precipitate was separated by filtration, washed with methanol and dried under high vacuum to give yellowish solid (98 mg, 87%), mp 126–127 °C. δ_H ($CDCl_3$): 1.14 (s, 3H, C–CH_3), 1.16 (s, 3H, C–CH_3), 2.36 (d, $^2J_{H,H}$ 13.4, 1H, CH_2), 2.44 (d, $^2J_{H,H}$ 13.5, 1H, CH_2), 3.67 (s, 3H, O–CH_3), 3.80 (s, 3H, O–CH_3), 3.92 (s, 3H, O–CH_3), 4.31 (s, 1H, CH–O), 6.55 (d, $^3J_{H,H}$ 15.5, 1H, CH=C*H*–C), 7.50–7.64 (m, 5H, CH), 7.77 (s, 1H, CH), 7.84–7.87 (m, 1H, CH), 8.10–8.13 (m, 1H, CH), 8.61–8.70 (m, 2H, CH); δ_C ($CDCl_3$): 22.3 (C–CH_3), 26.8 (C–CH_3), 38.7 (*C*–CH_3), 49.3 (CH_2), 52.2 (O–CH_3), 53.5 (O–CH_3), 59.0 (O–CH_3), 74.4 (C–N), 107.9 (CH–O), 113.4 (*C*=C–O), 122.7 (CH), 123.2 (CH), 125.0 (CH), 125.1 (CH), 126.7 (2×CH), 126.8 (CH), 126.9 (CH), 127.4 (CH), 128.8 (CH), 130.4 (C_{Ar}), 130.5 (C_{Ar}), 130.9 (C_{Ar}), 132.0 (C_{Ar}), 133.7 (C_{Ar}), 134.7 (CH_{Ar}), 150.9 (C=*C*–O), 160.0 (C=O), 162.7 (C=O); IR (KBr): 725, 746, 1088, 1117, 1142, 1201, 1215, 1290, 1331, 1435, 1666, 1711, 1755, 2839, 2870, 2902, 2951, 2970, 2997, 3022,

3061; Calcd for $C_{29}H_{30}NO_6$ (MH^+) 488.2073, HRMS found 488.2071. Compound was subjected to X-ray diffraction.

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10. Nitrone **4a** was isolated by gradient elution column chromatography $Et_2O \rightarrow Et_2O$/EtOAc (1/1); nitrone **5** was isolated by precipitation of crude reaction mixture in hexane and subsequent separation of formed precipitate.
11. With exception of temperature; 60 °C was necessary to decrease the degree of decomposition.
12. Based on the NMR spectra of crude reaction mixture.
13. *SHELXTL, Version 5.10*; Bruker AXS: Madison, WI, USA, 1997.
14. Carbon (grey), oxygen (red) and nitrogen (blue) atoms are drawn as principal ellipses (80% probability level); hydrogen atoms are drawn as fixed-size spheres (cyan).
15. Crystallographic data for compounds **3c** (CCDC deposition number 741761), **5**(CCDC deposition number 741762) **7** (CCDC deposition number 741763) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
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