

Unexpected formation of polycyclic oxygen-containing spiro-heterocycles in the reactions of 2,4-dihydro-3H-pyrrol-3-one 1-oxides with benzaldehyde

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DOI: 10.1016/j.mencom.2008.11.002

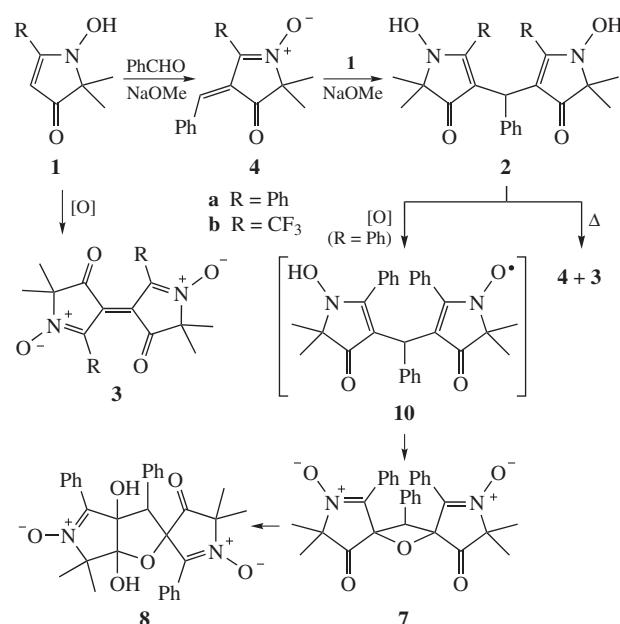
The polycyclic oxygen-containing spiro-heterocycles 6-oxa-2,9-diazadispiro[4.1.4.1]dodeca-1,8-diene-4,11-dione 2,9-dioxide and 3,3a,6,6a-tetrahydrospiro(furo[2,3-*c*]pyrrole-2,3'-pyrrol)-4'(5'H)-one 1',5-dioxide were formed in the reactions of 2,4-dihydro-3H-pyrrol-3-one 1-oxide with benzaldehyde.

Enhydroxyaminones (β -oxonitrones) are insufficiently explored organic compounds. Their reactions with nucleophiles and electrophiles have been described.^{1–5} An electrophilic attack in these compounds is usually directed to the enamine carbon or the oxygen of the hydroxyl group.¹ In particular, it was previously reported that the reaction of 1-hydroxy-2,2-dimethyl-1,2-dihydropyrrol-3-one derivatives **1** with benzaldehyde leads to the formation of condensation products of two pyrroline molecules with one aldehyde molecule **2**.¹ A similar transformation was observed in the case of another C–H acid, which formally contains an enhydroxylaminone moiety, 3-phenyl-(4*H*)-isoxazol-5-one.⁶ In this case, an intermediate compound, the product of crotonic-type condensation was isolated along with the condensation product of two isoxazolone molecules with one benzaldehyde molecule.

The modifications of enhydroxyaminones by insertion of different substituents to the carbon atom between carbonyl and nitrone groups is of interest because the resulting compounds can be the precursors of stable vinyl nitroxides.^{4,5} Here, we describe the condensation reaction⁵ of enhydroxyaminones, the derivatives of 1-hydroxy-2,2-dimethyl-1,2-dihydropyrrol-3-ones **1**.

The structures of products and their ratio are strongly dependent on the reaction conditions, in particular, on the excess of a base (sodium methylate). The reaction is complicated by the oxidation of both starting pyrrolines **1** into dimers **3**⁷ and the condensation products formed (Table 1).[†]

The products of crotonic-type condensation **4** and compounds **2**, formed as a result of the further pyrroline **1** anion



Scheme 1

addition to **4**, were evolved from the reaction of pyrrolines **1** with benzaldehyde under argon (Scheme 1). Products **2** decomposed on heating (for example, during recrystallization) to form compounds **4** and dimers **3**. The spectral characteristics of **2**

Table 1 Optimized conditions for the synthesis of compounds **2a,b**, **4a,b**, **7** and **8**.

Product	MeONa/ mmol	t/h	Atmo- sphere	Sorbent/eluent	Yield (%)
2a	1.0	4	Ar	—	35
2b	0.5	24	Ar	—	50
4a	0.5	48	Ar	alumina/CHCl ₃ , then silica gel/C ₆ H ₆ –Et ₂ O (4:1)	25
4b	0.5	48	Ar	silica gel/CHCl ₃ –MeOH (30:1)	30
7	0.5	48	Air	silica gel/CHCl ₃	10
8	3.4	48	Air	silica gel/CHCl ₃ , CHCl ₃ –MeOH (25:1)	6

[†] Compounds **11**,⁸ **1a,b**⁹ were synthesized as described elsewhere.

Typical procedure for the reaction of pyrrolines **1** with benzaldehyde. A solution of 1.0 mmol pyrroline **1**, 0.16 ml (1.5 mmol) benzaldehyde and MeONa in 6 ml MeOH was kept at room temperature, then evaporated. The residue was diluted with 4 ml of water, extracted with diethyl ether (in the case of **2a** the solution was acidified with 5% HCl to pH 6 before extraction), the combined extracts were evaporated. For isolation of **2a,b** the residue was triturated with small amount of CHCl₃ and the precipitate of **2a,b** was filtered off. Compounds **4a,b**, **7**, **8** were isolated from filtrate by column chromatography/TLC on silica gel or alumina.

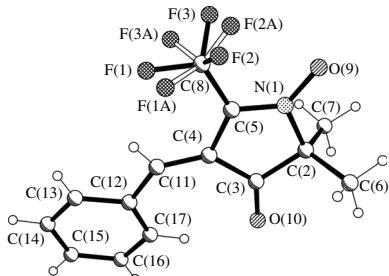
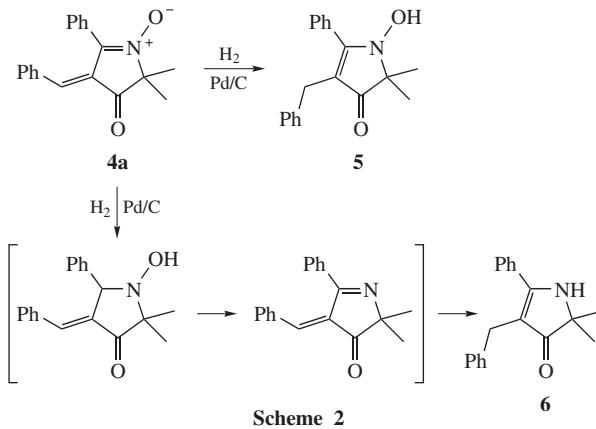


Figure 1 Molecular structure of **4b** (CF_3 group is disordered over two positions with occupancies 0.62:0.38).

differ from those published previously [only IR and ^1H NMR spectra of **2** ($\text{R} = \text{Ph}, \text{Me}$) were given],¹ but unambiguously prove the ascribed structure (see Online Supplementary Materials). The structure of **4b** was proven by X-ray diffraction analysis (Figure 1).[‡] Compound **4a** was isolated as a mixture of *Z*- and *E*-isomers, which were able to turn into each other in solution, this process accelerates in the presence of silica gel. The *E*-isomer was evolved from the mixture by recrystallization, the ^1H and ^{13}C NMR spectra of *Z*-isomer were obtained by a comparison of spectra of a mixture with those for the individual *E* isomer.



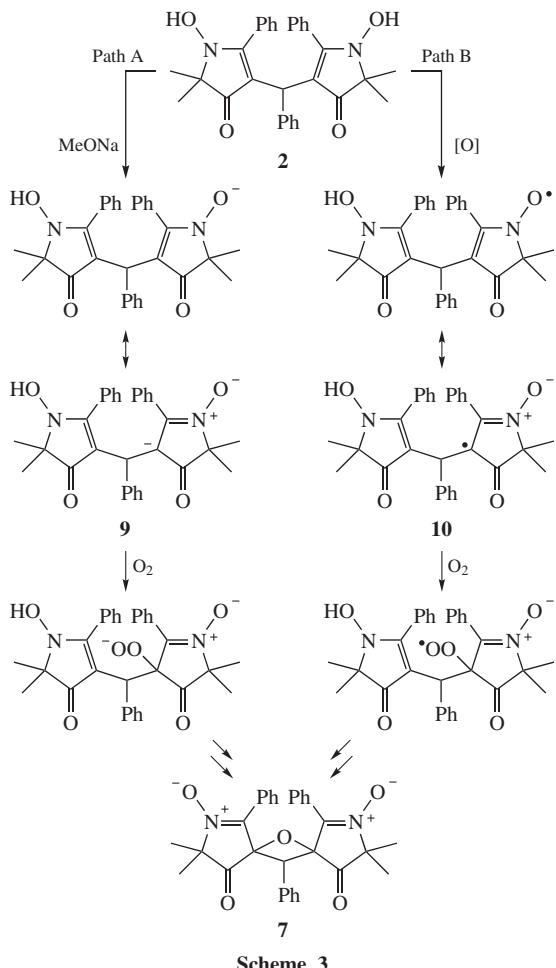
[‡] X-ray diffraction data.

(4*Z*)-4-Benzylidene-2,2-dimethyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrrol-3-one **4b**: $\text{C}_{14}\text{H}_{12}\text{F}_3\text{NO}_2$, $M = 283.25$, monoclinic, space group $P2_1/n$; $a = 11.8660(4)$, $b = 8.5615(4)$ and $c = 13.2120(6)$ Å, $\beta = 99.5340(10)^\circ$, $V = 1323.68(10)$ Å 3 , $T = 296 \pm 2$ K, $Z = 4$, $d_{\text{calc}} = 1.421$ g cm $^{-3}$; $\mu(\text{MoK}\alpha) = 0.123$ mm $^{-1}$; $F(000) = 584$, reflections measured/independent, 12563/4203; $R_{\text{int}} = 0.0186$; the final indexes are $S = 1.117$, $R_1 = 0.0928$, $wR_2 = 0.1980$ for all reflections and $R_1 = 0.0578$, $wR_2 = 0.1818$ for 2482 $F_0 > 4\sigma$.

3,3,10,10-Tetramethyl-1,8,12-triphenyl-6-oxa-2,9-diazadispiro[4.1.4.1]-dodeca-1,8-diene-4,11-dione 7: $\text{C}_{31}\text{H}_{28}\text{N}_2\text{O}_5$, $M = 508.55$, orthorhombic, space group $P2_12_12_1$; $a = 10.186(3)$, $b = 14.540(4)$ and $c = 17.849(5)$ Å, $V = 2643.7(12)$ Å 3 , $T = 296 \pm 2$ K, $Z = 4$, $d_{\text{calc}} = 1.278$ g cm $^{-3}$; $\mu(\text{MoK}\alpha) = 0.096$ mm $^{-1}$; $F(000) = 1072$, reflections measured/independent, 3238/3238; the final indexes are $S = 1.095$, $R_1 = 0.1256$, $wR_2 = 0.1630$ for all reflections and $R_1 = 0.0626$, $wR_2 = 0.1380$ for 1914 $F_0 > 4\sigma$.

3a,6a-Dihydroxy-5',5',6,6-tetramethyl-2,2',3-triphenyl-3a,6,6a-tetrahydrospiro[furo[2,3-c]pyrrole-2,3'-pyrrol]-4'($5'\text{H}$)-one 1',5-dioxide **8**: $\text{C}_{31}\text{H}_{30}\text{N}_2\text{O}_6$, $M = 526.56$; monoclinic, space group $P2_1/c$; $a = 14.490(6)$, $b = 10.932(6)$ and $c = 17.138(8)$ Å, $\beta = 101.70(4)^\circ$, $V = 2658(2)$ Å 3 , $T = 293(2)$ K, $Z = 4$, $d_{\text{calc}} = 1.316$ g cm $^{-3}$; $\mu(\text{MoK}\alpha) = 0.092$ mm $^{-1}$; reflections measured/independent, 3895/3713; $R_{\text{int}} = 0.0418$; the final indexes are $R_1 = 0.1354$, $wR_2 = 0.2601$ for all reflections and $R_1 = 0.0775$, $wR_2 = 0.1883$ for $I > 2\sigma(I)$.

CCDC 622728, 675095 and 680017 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2008.



Scheme 3

Catalytic hydrogenation of the mixture of isomers **4a** leads to compounds **5**, **6**, perhaps, in the result of non-selective hydrogenation of C=C and C=N bonds. In the latter case, the subsequent reduction of the C=C bond and dehydration apparently leads to compound **6** (Scheme 2).[§]

When the reaction of pyrroline **1a** with benzaldehyde was carried out in the presence of air, the oxidation products, oxetane **7** and tetrahydrofuran derivative **8**, were isolated along with usual condensation products **2a** and **4a** (Scheme 1). The structures of **7** and **8** were proven by X-ray crystallography (Figures 2 and 3).[‡]

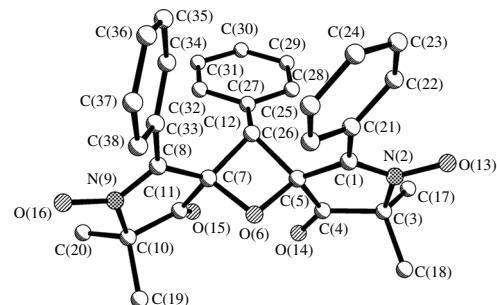
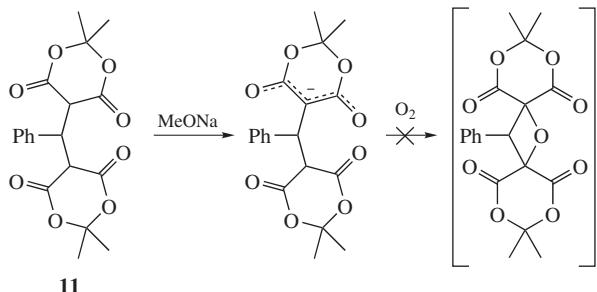


Figure 2 Molecular structure of **7** (H-atoms are not shown).

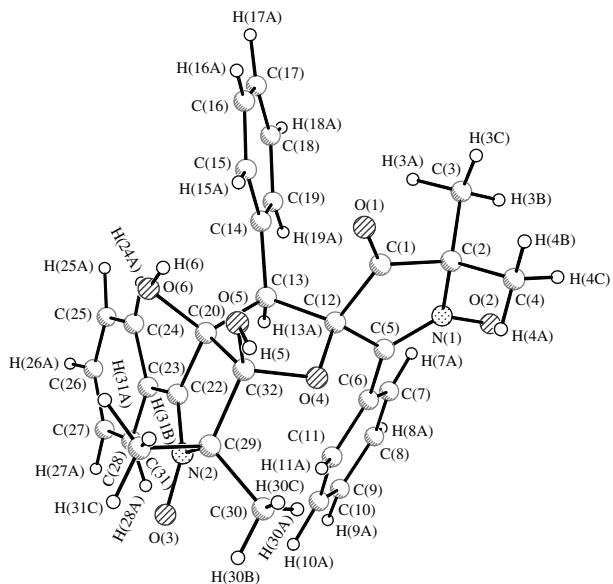
[§] 4-Benzyl-1-hydroxy-2,2-dimethyl-5-phenyl-1,2-dihydro-3*H*-pyrrol-3-one **5** and 4-benzyl-2,2-dimethyl-5-phenyl-1,2-dihydro-3*H*-pyrrol-3-one **6**. A mixture of isomers **4a** (0.08 g, 0.27 mmol) was hydrogenated in MeOH over Pd/C for 1 h at atmospheric pressure. Then the catalyst was filtered off and the solution was evaporated. Compounds **5** and **6** were separated by silica gel column chromatography [hexane-Et₂O (1:1), Et₂O].

For characteristics of compounds **2a,b**, **4a,b** and **5-8**, see Online Supplementary Materials.



Scheme 4

It could be supposed that oxetane **7** originated from either anion **9** or radical **10** (Scheme 3). Compound **11**, for which the radical path is improbable, is not oxidized under the same conditions, so this indirectly testifies against the ionic path A

Figure 3 Molecular structure of **8**.

(Scheme 4). Radical path B is supported by the fact that pyrrolines **1** easily generate vinylnitroxides on oxidation.⁷

The relative content of compound **8**, which presumably formed from **7**, increased with the concentration of a base and the reaction time being prolonged (Scheme 1).

Note that the IR spectrum of compound **8** is almost identical to those ascribed to compound **2a**,¹ that means that the structure of the latter was determined incorrectly.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2008.11.002.

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Received: 16th April 2008; Com. 08/3122