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From 1,4-diketones to *N*-vinyl derivatives of 3,3′-bipyrroles and 4,8-dihydropyrrolo[2,3-*f*]indole in just two preparative steps

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Abstract—Dioximes of hexane-2,5-dione and cyclohexane-1,4-dione react with acetylene in an autoclave (KOH/DMSO, 100 °C, 1 h, initial pressure 14 atm) to give 2,2′-dimethyl-1,1′-divinyl-[3,3′]bipyrrole and 1,5-divinyl-4,8-dihydropyrrolo[2,3-*f*]indole in 12% and 6% yields, respectively, thus exemplifying a very simple, straightforward route to inaccessible or unknown pyrrolic assemblies.

Bipyrrolic structures are widespread in Nature and are constituents of prodigiosins and corrins, including vitamin B_{12} and its analogs.[1] However, this refers mainly to 2,2′-bipyrrole derivatives, whereas other pyrrolic assemblies, particularly 3,3′-bipyrroles, have remained understudied for a long time whilst having only minor importance among the bipyrroles.[1,2] Interest in these bipyrroles appeared as recently as the 1980's due to the need for the synthesis of the antitumor agent CC-1065, where 3,3′-bipyrroles were building blocks.[3,4] The strategy for their synthesis was based on a sequential building up of the pyrrole rings using several preparative steps.[3]

Meanwhile, a straightforward approach to 3,3′-bipyrrole assemblies could be achieved using the known two step transition from ketones to pyrroles via the reaction of ketoximes with acetylene in the presence of the KOH/DMSO system, often referred to as the Trofimov reaction.[5,6]

To prove the feasibility of this approach, we chose two 1,4-diketones, namely hexane-2,5-dione **1** and cyclohexane-1,4-dione **9**, as representing open chain and cyclic members of the series, and subjected their dioximes, **2**[7] and **10**,[8] to the reaction with acetylene.[9]

A number of alternative pathways to the required reaction could interfere. Thus, in the case of dioxime **2**, three bipyrroles could be formed (Scheme 1) due to the rearrangements[5,10] involving both the methylene and methyl groups in the intermediates **3**–**5**.

The target 2,2′-dimethyl-1,1′-divinyl-[3,3′]bipyrrole **6** was isolated by column chromatography in 12% yield (not optimized) as the major product.[11] The structurally isomeric bipyrroles **7** and **8** were only minor components of the reaction mixture, because they would have been built up with the participation of the methyl groups of the intermediates **3**–**5**, which are less reactive compared to the competing methylene groups.[5,10] Thermodynamics may also contribute to the product distribution, since the major isolated isomer **6** is the most conjugated.

In the case of cyclohexane-1,4-dione dioxime **10**, under the same conditions, the unconjugated bipyrrolic cyclophane **13** was isolated in 6% yield (not optimized),[12] instead of the expected conjugated 3,3′-linked bipyrrole system **14** (Scheme 2).

The structure of the 1,5-divinyl-4,8-dihydropyrrolo[2,3*f*]-indole **13** followed from a 2D NOESY experiment, which showed cross-peaks between the protons H_3 and H_4 (H_7 and H_8). Quantum chemical calculations

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Keywords: 3,3′-Bipyrroles; Pyrroloindoles; Dioximes; Acetylene; Superbases.

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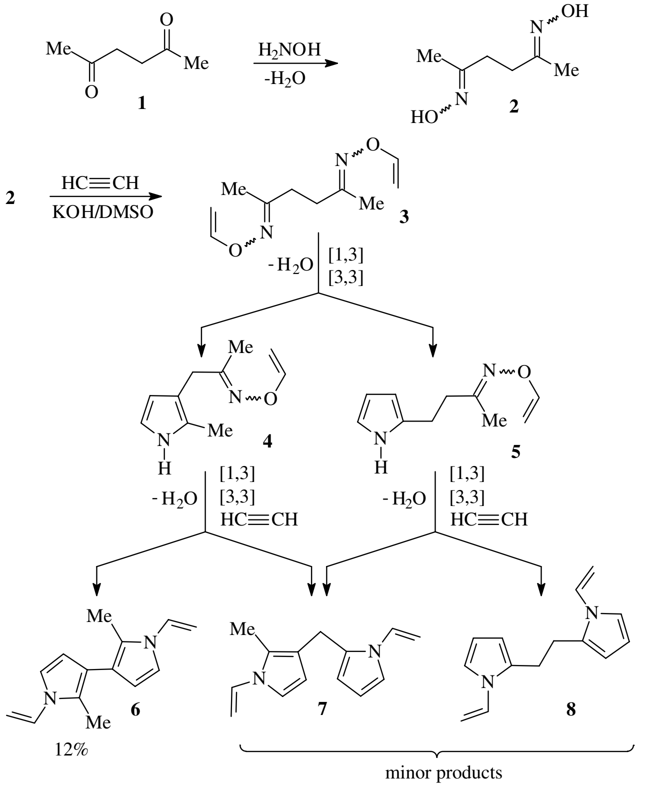
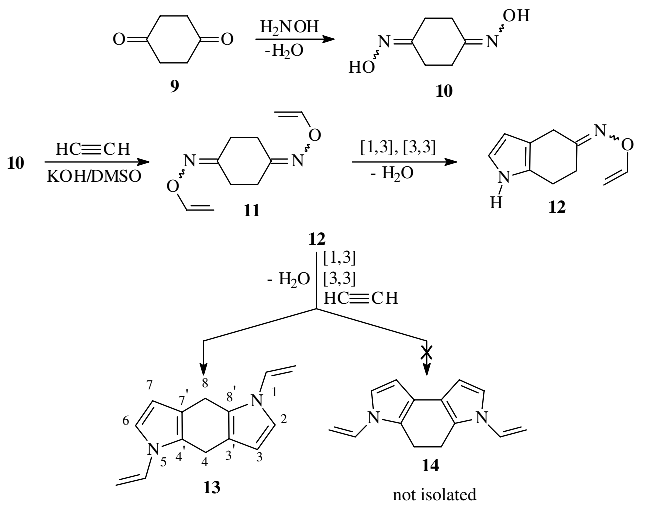


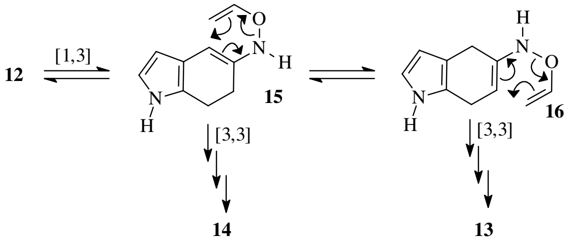
Scheme 1.



Scheme 2.

[B3LYP/6-311++G(d,p)] confirmed the higher stability $(\Delta E = 1.33\,\mathrm{kcal\,mol^{-1}})$[13] of isomer **13** as compared to isomer **14**.

The reason why structure **14** becomes thermodynamically less favorable relative to structure **13** may be due to the H–H repulsion between the two adjacent methylene groups in the cyclohexane ring, which distorts the coplanarity of the whole tricyclic skeleton [B3LYP/6-311++G(d,p) data], thus decreasing the pyrrole–pyrrole conjugation. It turns out that, according to the quantum mechanical calculation, **13** is planar including the two vinyl groups, the latter deviating out of the plane by no more than 1°. The thermodynamic stabilization of **13** may originate from transannular interactions of the pyrrole moieties as supported by the absence of nodes in the HOMO of **13** between C_3'–C_8' $\mathrm{kcal\,mol^{-1}}$ and C_4'–C_7'.



Scheme 3.

Interestingly, of the two key intermediate vinyloxyhydroxylamines **16** and **15** (Scheme 3),[5,10] the former one (**16**) leading to **13** is 0.47 $\mathrm{kcal\,mol^{-1}}$ less stable than its isomer **15** [B3LYP/6-311++G(d,p) calculations for the most stable conformations], that is, this particular kinetic factor works against the experimental result.

In conclusion, the reaction of 1,4-diketone dioximes with acetylene in the KOH/DMSO system provides a direct access to *N*-vinyl-3,3′-bipyrroles and 4,8-dihydropyrrolo[2,3-*f*]indoles, which are promising pharmacophores, monomers, and building blocks for biologically important molecules.

Acknowledgements

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7. Compound **2**. $NH_2OH{\cdot}HCl$ (7.59 g, 109 mmol) and CH_3COONa (8.94 g, 109 mmol) in MeOH (20 mL) were stirred for 20 min at room temperature. Then hexane-2,5-dione **1** (5.00 g, 44 mmol) was added, and stirring was continued for 3 h. The NaCl precipitate was filtered off and washed with Et_2O. The filtrate and the ether solution were combined and neutralized with an excess of a concentrated aqueous solution of K_2CO_3. After addition of ether (50 mL) and vigorous shaking, the organic layer was separated, washed with water (2 × 5 mL), and dried over anhyd K_2CO_3. After removal of solvents in vacuo (water-jet pumped rotary evaporator), dioxime **2** (2.05 g, 32%) was obtained as a white powder, mp 144 °C (from MeOH). ^1H NMR (DMSO-d_6): δ 10.32 (s, 2H, OH), 2.29 (s, 4H, CH_2), 1.73 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6): δ 155.07 (C=N), 32.70 (CH_2), 13.74 (Me). IR (KBr) ν_{max}: 3246, 2922, 1673, 1576, 1429, 1375, 1308, 1203, 945, 825, 762, 731, 616, 483 cm^{-1}.
8. Compound **10**. To the mixture of cyclohexane-1,4-dione **9** (7.00 g, 62 mmol), $NH_2OH{\cdot}HCl$ (10.84 g, 156 mmol), EtOH (35 mL), and water (3 mL), finely ground NaOH (6.24 g, 156 mmol) was gradually added while stirring. After addition of the NaOH, stirring was continued for 30 min, then mixture was poured into cold water (150 mL), and the precipitate was filtered off and washed with water. After drying under vacuum (1 Torr) dioxime **10** (6.90 g, 78%) was obtained as a white powder, mp 192–196 °C (from Et_2O). ^1H NMR (DMSO-d_6): δ 10.40, 10.38 (s, 2H, OH), 2.51 (m, 4H, H_{syn}), 2.39 (m, 4H, H_{anti}). ^{13}C NMR (DMSO-d_6): δ 156.21, 155.72 (C=N), 29.23, 26.49, 23.44, 20.99 (CH_2). IR (KBr) ν_{max}: 3198, 3075, 2861, 1659, 1487, 1418, 1324, 1275, 1212, 1175, 1121, 1055, 1001, 974, 953, 926, 843, 778, 711, 642, 534 cm^{-1}.
9. General procedure for the synthesis of 2,2′-dimethyl-1,1′-divinyl-[3,3′]bipyrrole **6** and 1,5-divinyl-4,8-dihydropyrrolo[2,3-*f*]indole **13**. Into a steel 0.5-L rotating autoclave, the dioxime (14 mmol), $KOH{\cdot}0.5H_2O$ (15% water content) (1.80 g, 28 mmol) and DMSO (50 mL) were loaded. The mixture was saturated with acetylene from a cylinder (14 atm) and heated at 100 °C whilst rotating for 1 h. After cooling to room temperature, the autoclave was discharged, and the reaction mixture was diluted with water (up to 100 mL) and extracted with Et_2O (4 × 30 mL). The ether extracts were washed with water (3 × 20 mL), dried over anhyd K_2CO_3 and filtered. After distilling off the ether, the products were isolated by column chromatography (basic Al_2O_3, hexane–ether, 2:1).
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11. Compound **6**. Yield 12%. Light yellow transparent liquid, n_D^{23} 1.5780. ^1H NMR ($CDCl_3$): δ 6.96 (d, 2H, $^3J_{4\text{–}5} = 3.1$ Hz, H_5), 6.89 (dd, 2H, $^3J_{AX} = 8.9$ Hz, $^3J_{BX} = 15.6$ Hz, H_X), 6.16 (d, 2H, H_4), 5.07 (dd, 2H, $^3J_{AB} = -0.9$ Hz, H_B), 4.63 (dd, 2H, H_A), 2.20 (s, 6H, Me). ^{13}C NMR ($CDCl_3$): δ 130.88 (C_α), 125.07 (H_2), 117.38 (H_5), 115.15 (H_4), 111.39 (H_3), 97.33 (H_β), 10.74 (Me). IR (thin film) ν_{max}: 2920, 1638 ($\nu C{=}C_{vin}$), 1560 ($C\text{–}C_{pyr}$), 1488 ($C\text{–}C_{pyr}$), 1424, 1378 ($C\text{–}C_{pyr}$), 1305 ($N\text{–}C_{vin}$), 1284, 961 ($\tau HC{=}CH$), 889, 857 (ωCH_2), 709 ($\delta C\text{–}H_{pyr}$), 589 ($\omega HC{=}CH$) cm^{-1}.
12. Compound **13**. Yield 6%. Yellowish needles, mp 188 °C (from Et_2O). ^1H NMR ($CDCl_3$): δ 7.00 (d, 2H, $^3J_{4\text{–}5} = 2.8$ Hz, H_5), 6.86 (dd, 2H, $^3J_{AX} = 9.2$ Hz, $^3J_{BX} = 15.8$ Hz, H_X), 6.17 (d, 2H, H_4), 5.08 (dd, 2H, H_B), 4.63 (dd, 2H, H_A), 3.74 (s, 4H, CH_2). ^{13}C NMR ($CDCl_3$): δ 130.48 (C_α), 126.44 ($C_{4',8'}$), 116.19 ($C_{2,6}$), 115.31 ($C_{3',7'}$), 109.04 ($C_{3,7}$), 96.77 (C_β), 21.87 (CH_2). IR (KBr) ν_{max}: 1640 ($\nu C{=}C_{vin}$), 1572 ($C\text{–}C_{pyr}$), 1486 ($C\text{–}C_{pyr}$), 1377 ($C\text{–}C_{pyr}$), 1306 ($N\text{–}C_{vin}$), 1262, 964 ($\tau HC{=}CH$), 862 (ωCH_2), 711 ($\delta C\text{–}H_{pyr}$), 585 ($\omega HC{=}CH$) cm^{-1}.
13. The computational and structural details of the compounds **13** and **14** will be considered elsewhere.