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# Easy α- to β-migration of an enol moiety on a pyrrole ring

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**Abstract**—Functionalized pyrrolic enols, 2-(2,2-dicyano-1-hydroxyethenyl)-1-methylpyrroles, synthesized from 2-ethenylpyrroles by a nucleophilic SEt-OH exchange, upon heating (75–142 °C) are readily rearranged to their 3-isomers in near to quantitative yield. The inter or intramolecular auto-protonation of a pyrrole ring by the acidic enol hydroxyl to form a mesomeric pyrrolium cation or zwitterion is suggested to be a key step in the rearrangement.


Functionalized *C*-vinylpyrroles are key structural units of natural chromophores such as chlorophylls, hemoglobin, vitamin $B_{12}$, and related macrocyclic tetrapyrrole pigments which play vital roles in plants and animals[1] as well as being valuable intermediates for the construction of diverse pyrrole assemblies.[2]

Among functional vinyl compounds, enols and their reactive cationic intermediates are under extensive investigation[3] (due to their activity in DNA damage,[4] transformations induced by $B_{12}$-dependent enzymes[5] and ribonucleotide reductase[6]), attention being particularly focused on heterocyclic enols.[3c]

The last two decades have witnessed a steadily growing understanding of the structure and reactivity of isolable enols,[3a,7] normally fleetingly existing tautomers of aldehydes and ketones.

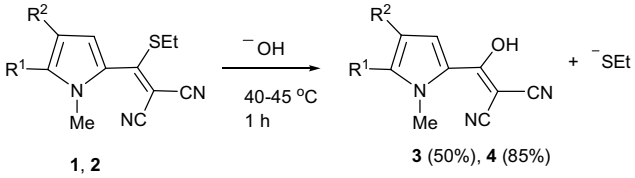
In spite of recent successful syntheses of stable enols of the furan, thiophene[3c], and pyridine[8] series, attempts to synthesize the corresponding representative with 2-pyrrolyl substituent have failed; instead, the tautomeric ketone was isolated in 7% yield along with a mixture of unidentified products.[3c]

Thus, the synthesis of vinylpyrroles with an enol function and study of their reactivity represent important issues in both vinylpyrrole and enol chemistry as well as in a broader sense.

In this letter, we report a novel synthesis of functionalized 2-vinylpyrroles **3** and **4** and an unprecedentedly easy migration of their enol moieties from α- to β-position of the pyrrole ring.

The stable enols **3** and **4**, 2-(2,2-dicyano-1-hydroxyethenyl)-1-methylpyrroles, were synthesized from 2-(2,2-dicyano-1-ethylthioethenyl)-1-methylpyrroles **1** and **2** by the easy exchange of their ethylthio group for hydroxyl by the action of NaOH (MeOH–$H_2O$, 40–45 °C, 1 h), yields being 50% and 85%, respectively (Scheme 1).[9]

Upon heating (75–142 °C), enols **3** and **4** were found to rearrange to their 3-isomers **5** and **6** (Scheme 2).




**1**, **2** → **3** (50%), **4** (85%)

**1**, **3**: $R^1 = R^2 = H$
**2**, **4**: $R^1$-$R^2 = (CH_2)_4$

**Scheme 1.**

*Keywords*: 2-Vinylpyrroles; Ethylthio group; Hydroxide; Enols; α- to β-Migration.
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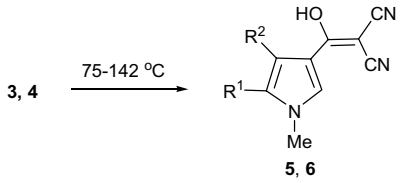



**Scheme 2.**

Thus, enol **3** after 5 min boiling in benzene, toluene or *o*-xylene contained correspondingly 3%, 4%, and 8% of isomer **5** ($^1$H NMR monitoring), while refluxing **3** for 1 h in toluene resulted in 60% conversion of **3** to **5**, and in *o*-xylene the conversion was quantitative. In DMSO-$d_6$, after 21 h heating at 110 °C, the ratio of **3**:**5** was 1:2.[10]

Surprisingly, fast and complete rearrangement occurred with enol **4**, which was converted into **6** simply upon crystallization from benzene.[11]

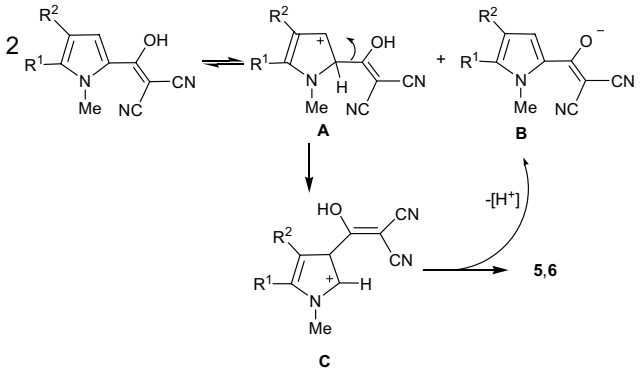
Although enol **3** was previously claimed to have been synthesized by another route[12], though characterized only by one OH stretching band in aqueous(?) $NaHCO_3$ solution, no migration of its enol moiety was reported.

It should be emphasized that the rearrangement observed is unique for pyrrole chemistry, both because of its ease and preferred position. Indeed, thermal substituent migration in the pyrrole ring is known to proceed at much higher temperatures (300–700 °C) with preferred formation of α-isomers.[13] Thus, for instance, 1-(2-pyridyl)pyrrole rearranges at 350 °C to 2-(2-pyridyl)pyrrole and 3-(2-pyridyl)pyrrole in a ratio of 5:1, at 710 °C only the 2-isomer is formed.[13b,14,15] The latter is stable at 710 °C, whereas 3-(2-pyridyl)pyrrole is readily converted into the 2-isomer.[13b,15] Similarly, at 700 °C, only the methyl substituent of 1-methyl-2-(2-pyridyl)pyrrole migrates to give 2-methyl-5-(2-pyridyl)pyrrole.[13b,16]

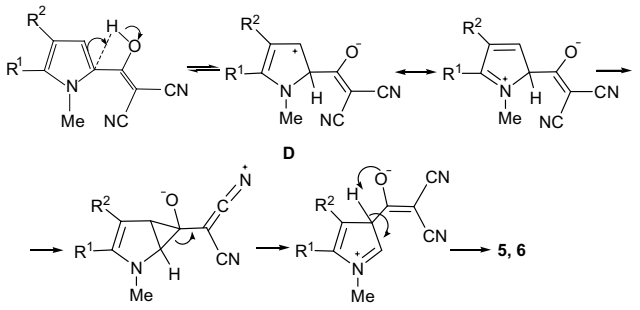
Apparently, the easy α- to β-migration of an enol moiety in **3** and **4** is due to (i) the enhanced acidity of the hydroxyl function (the effect of the two strong electron-withdrawing CN groups in a conjugated system, actually the enol moiety in **3** and **4** is a 'vinylog' of cyanic acid, HOCN) and (ii) the sensitivity of the pyrrole ring towards protonation.

Therefore, a tentative mechanism for the rearrangement can be proposed as follows (Scheme 3): first self-protonation at the α-position of the pyrrole ring occurs to give the mesomeric cation **A**, in which 1,2 vinyl migration takes place, the process being complete with proton transfer from the protonated product **C** to the anion **B**.

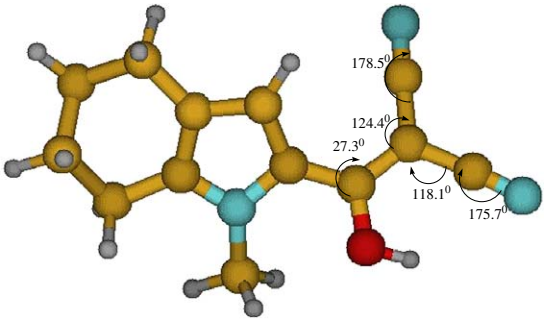
Apparently, the alternative intramolecular auto-protonation of the pyrrole ring to generate the zwitterion **D**, further rearranging to the products **5** and **6** (Scheme 4) may also not be fully excluded, particularly for the dilute solutions (~1%) employed in this work. In the latter case, the generally unfavorable proton transfer in the four-membered ring may be compensated by the formation of the stable mesomeric zwitterion **D**.



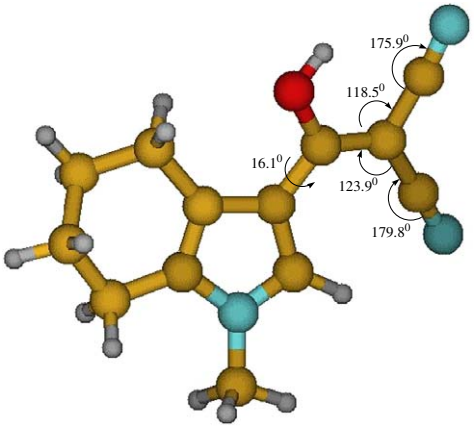

**Scheme 3.**




**Scheme 4.**




**4** (2.1 kcal/mol)




**6** (0.0 kcal/mol)

**Figure 1.** Computed preferred conformations and relative energies of the α- (**4**)- and β- (**6**)-isomers (MP2//HF/6-311++G**).

Support for the crucial role of the hydroxyl proton in the rearrangement is the fact that no migration of the vinyl group occurs for the ethylthio analogs **1** and **2** under the same conditions.

The computed (MP2//HF/6-311++G**)[17] energy difference for isomers **4** and **6** (2.1 kcal/mol, Fig. 1), though in favor of the β-isomer **6**, is rather small to be considered as a driving force of the rearrangement, thus implying the kinetic nature of the migration of the enol moiety.

The computed preferred conformations of the α- and β-isomers (**4** and **6**) are essentially non-planar (Fig. 1) with the hydroxyl group turned outward from the pyrrole ring in the β-isomer **6** which hinders the reverse autoprotonation. Besides, the acidity of the hydroxyl group of the β-isomer **6** is likely to be lower compared to that of the α-isomer **4** due to the smaller positive charge at the pyrrole β-position.

The proposed mechanisms (Schemes 3 and 4) agree well with the reactivity difference of the starting enols **3** and **4**: the electron-donor (tetramethylene) moiety attached to positions 2 and 3 of the tetrahydroindole derivative **4** enhances the protophilicity of the pyrrole ring as compared to the unsubstituted enol **3**.

## Acknowledgments

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9. To a solution of **1** (100 mg, 0.46 mmol) in 4 mL of MeOH, NaOH (37 mg, 0.92 mmol) in water (0.5 mL) was added at 40–45 °C and the mixture was kept at this temperature for 1 h. After cooling and evaporation of the solvents in vacuo, the residue was dissolved in water (3 mL) and acidified with aqueous HCl (10%) to pH 3. The solution was extracted with $CHCl_3$ and the extract was dried over $CaCl_2$. After evaporation of the solvent 2-(2,2-dicyano-1-hydroxyethenyl)-1-methylpyrrole **3** (40 mg, 50% yield) was obtained as brown crystals, mp 114–115 °C; IR (KBr): 3073 (OH), 3114, 760, 698 (pyrrole CH), 2227, 2205 (CN), 1550 (C=C), 1508, 1482, 1401 $cm^{-1}$ (pyrrole ring); $^1H$ NMR (400.13 MHz, DMSO-$d_6$) $\delta$ 6.83 (dd, $J = 1.8$, 2.4 Hz, H-5, 1H), 6.70 (dd, $J = 1.8$, 3.8 Hz, H-3, 1H), 5.96 (dd, $J = 2.4$, 3.8 Hz, H-4, 1H), 3.72 (s, NMe, 3H); (400.13 MHz, HMPA) $\delta$ 8.20 (br s, OH, 1H); $^{13}C$ NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 178.5 (=C–OH), 129.2, 127.0, 113.7, 106.3 (pyrrole ring), 122.3, 120.9 (CN), 47.7 [=*C*$(CN)_2$], 36.0 (NMe). Anal. Calcd for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.26%. Found: C, 62.72; H, 4.00; N, 24.15%.
   To a solution of **2** (50 mg, 0.18 mmol) in 3 mL of MeOH, NaOH (14 mg, 0.36 mmol) in water (0.5 mL) was added at 40–45 °C and the mixture was kept at this temperature for 1 h. After cooling and evaporation of the solvents in vacuo, the residue was dissolved in water (3 mL) and acidified with aqueous HCl (10%) to pH 3. The precipitated solid was filtered off, washed with water and dried to give 35 mg (85% yield) of 2-(2,2-dicyano-1-hydroxyethenyl)-1-methyl-4,5,6,7-tetrahydroindole **4** as an orange powder, mp 172–173 °C; UV [$\lambda_{max}$, nm, ($\log_\varepsilon$), ethanol]: 255 (3.83), 328 (4.33); IR (KBr): 3030 (OH), 2216, 2201 (CN), 1569 (C=C), 1520, 1476, 1438 (pyrrole ring), 753, 702 $cm^{-1}$ (pyrrole CH); $^1H$ NMR (400.13 MHz, DMSO-$d_6$) $\delta$ 6.56 (s, H-3, 1H), 3.47 (s, NMe, 3H), 2.49 (m, $CH_2$-7, 2H), 2.39 (m, $CH_2$-4, 2H), 1.75 (m, $CH_2$-6, 2H), 1.64 (m, $CH_2$-5, 2H); (400.13 MHz, HMPA) $\delta$ 6.81 (br s, OH, 1H); $^{13}C$ NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 175.4 (=C–OH), 137.2, 124.0, 117.9, 115.6 (pyrrole ring), 118.2, 117.3 (CN), 52.8 [=*C*$(CN)_2$], 32.1 (NMe), 27.9, 22.5, 22.4, 21.6 (cyclohexane ring). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49%. Found: C, 68.91; H, 5.88; N,18.46%.
10. 3-(2,2-Dicyano-1-hydroxyethenyl)-1-methylpyrrole **5**: 3 mg of **3** in 0.5 mL of DMSO-$d_6$ was heated at 110 °C for 21 h in an NMR spectrometer ampoule to give a 1:2 mixture of **3** and **5**. $^1H$ NMR of enol **5** (400.13 MHz, DMSO-$d_6$) $\delta$ 7.60 (dd, $J = 1.8$, 2.0 Hz, H-2, 1H), 6.90 (dd, $J = 2.0$, 2.9 Hz, H-5, 1H), 6.63 (dd, $J = 1.8$, 2.9 Hz, H-4, 1H), 3.70 (s, NMe, 3H); $^{13}C$ NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 178.5 (=C–OH), 127.5, 124.2, 115.9, 109.4 (pyrrole ring), 121.5, 117.5 (CN), 53.3 [=*C*$(CN)_2$], 36.6 (NMe).
11. 2-(2,2-Dicyano-1-hydroxyethenyl)-1-methyl-4,5,6,7-tetrahydroindole **6**. Crystallization of **4** (40 mg) from benzene (3 mL, 75 °C, 1 h) gave 36 mg (90% yield) of **6** as dark-brown lustrous small crystals, mp 179–180 °C; UV [$\lambda_{max}$, nm, ($\log_\varepsilon$), ethanol]: 303 (4.11); IR (KBr): 3044 (OH), 2223, 2205 (CN), 1533 (C=C), 1514, 1468, 1456 (pyrrole ring), 810, 714 $cm^{-1}$ (pyrrole CH); $^1H$ NMR (400.13 MHz, DMSO-$d_6$) $\delta$ 7.38 (s, H-2, 1H), 3.51 (s, NMe, 3H), 2.49 (m, $CH_2$-4,7, 4H), 1.75 (m, $CH_2$-6, 2H), 1.64 (m, $CH_2$-5, 2H); (400.13 MHz, HMPA) $\delta$ 5.00 (br s,

OH, 1H); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 180.0 (=C–OH), 130.4, 125.7, 117.7, 112.7 (pyrrole ring), 117.1, 115.3 (CN), 55.0 [=$C$(CN)$_2$], 33.2 (NMe), 27.9, 22.5, 22.4, 21.6 (cyclohexane ring). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49%. Found: C, 68.80; H, 5.56; N, 18.55%.

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