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Vinylic nucleophilic substitution in functionalized 2-vinylpyrroles: a route to a new family of stable enols

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Abstract—2-(2-Cyano-1-ethylthioethenyl)pyrroles easy exchange their ethylthio group for hydroxyl (NaOH, H_2O–methanol, 40–45 °C, 1 h) to give 2-(2-cyano-1-hydroxyethenyl)pyrroles, a new family of stable enols, in 50–94% yields. The vinylic nucleophilic substitution proceeds at the double bond of both the starting pyrroles and their cyclic isomers, 3-iminopyrrolizines. X-ray structure analysis and NMR spectra show the enols to be stabilized by exceptionally strong intramolecular H-bonding.

1. Introduction

The chemistry of pyrroles is attracting steady attention because these heterocycles play an important role in nature and, at the same time, possess rich synthetic potential making them valuable synthons for the design of novel materials for optoelectronics,[1] light-harvesting systems and photodynamic cancer diagnostics and therapy.[2] Vinylpyrroles are used for the synthesis of new heterocycles,[3,4] polymers,[5] photocatalysts and biologically active complexes.[6]

Our recent investigations into the reactivity of *C*-ethenylpyrroles with vinyl groups polarized by a push–pull combination of substituents, such as 2-(1-alkylthio-2-cyanoethenyl)pyrroles, have confirmed that these compounds possess synthetic potential, which may be utilized for a variety of synthetic needs.[4c,7]

Meanwhile, *C*-ethenylpyrroles with a hydroxyl group at the double bond still remain virtually unknown. In spite of recent successful synthesis of stable enols of furan and thiophene,[8] attempts to synthesize a corresponding representative with a 2-pyrrolyl substituent failed: instead the tautomeric ketone was isolated in 7% yield and a gamut of unidentified products.[8] Thus, the synthesis of vinylpyrroles with the enol function and their reactivity study represent important issues for both vinylpyrrole and enol chemistries.

As a rule, enols are unstable. However, their stability can be significantly increased by introduction of bulky substituents at the α-position or electron-withdrawing substituents at the β-position relative to the hydroxyl.[9]

Herein, we report on a general approach to the synthesis of a new family of stable enols of the *C*-ethenylpyrrole series based on nucleophilic substitution of an alkylthio group by hydroxyl in 2-(1-alkylthio-2-cyanoethenyl)pyrroles available from 2-pyrrolecarbodithioates.[10]

2. Results and discussion

We have found that in the presence of NaOH, the ethylthio group of *Z*-2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrroles **1a–d** is readily (H_2O/methanol, 1:2, 40–45 °C, 1 h) substituted by the ONa group to form enolates **2a–d** and upon acidification, the corresponding enols **3a–d** in 86–94% yield (Scheme 1).

The reaction is stereospecific (only one isomer with *syn*-disposition of hydroxyl and carbamoyl groups is formed) and chemoselective: the nitrile group is retained (although

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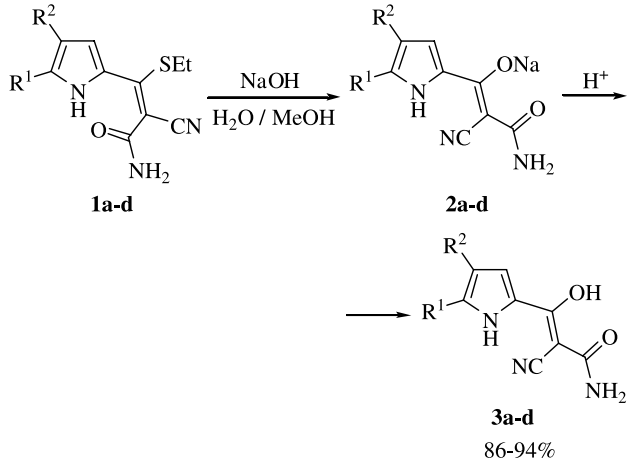
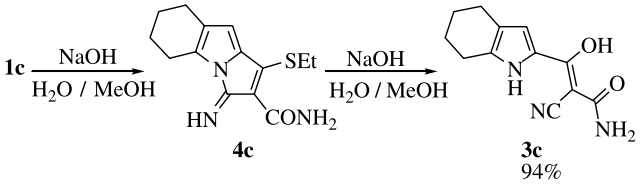


	R^1	R^2
1a-3a	*n*-Pr	E t
1b-3b	*n*-Bu	*n*-Pr
1c-3c	$(CH_2)_4$	
1d-3d	Ph	H

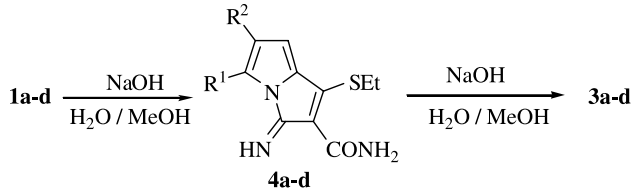
Scheme 1.

transformation of the nitrile to the carbamoyl function under the action of alkali in similar systems is known[11]). TLC monitoring shows the initial formation of intramolecular cyclization products, 3-iminopyrrolizines **4a–d**, which completely disappear by the end of the reaction. In the case of 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)-4,5,6,7-tetrahydroindole (**1c**), the corresponding 3-imino-pyrrolizine **4c** is quantitatively precipitated after addition of alkali and transformed into the enol **3c** by subsequent treatment with NaOH (H_2O/methanol, 1:2, 40–45 °C, 1 h) (Scheme 2).



Scheme 2.

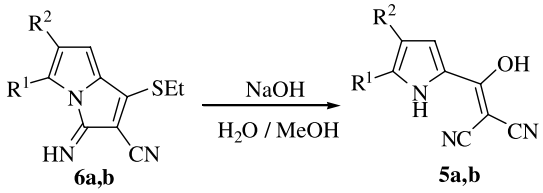
Apparently, the formation of enols **3a–d** occurs through nucleophilic substitution of the ethylthio group in 3-imino-pyrrolizines **4a–d** by hydroxide accompanied by the ring opening (Scheme 3).



	R^1	R^2
4a	*n*-Pr	Et
4b	*n*-Bu	*n*-Pr
4c	$(CH_2)_4$	
4d	Ph	H

Scheme 3.

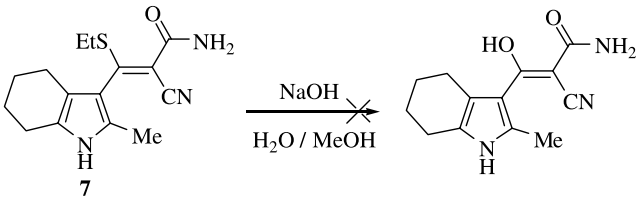
Another evidence for this reaction pathway is the synthesis of enols **5a**,**b** (78 and 90% yield, respectively) from 1-ethylthio-3-imino-2-pyrrolizinecarbonitriles **6a**,**b** under the same conditions (Scheme 4).



	R^1	R^2
5a,6a	*n*-Pr	Et
5b,6b	*n*-Bu	*n*-Pr

Scheme 4.

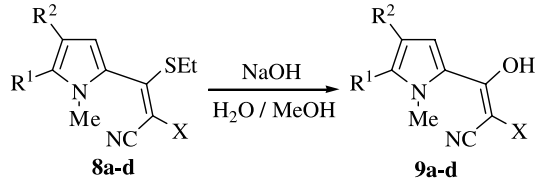
Correspondingly, no ethylthio–hydroxyl exchange in 3-(2-carbamoyl-2-cyano-1-ethylthioethenyl)-2-methyl-4,5,6,7-tetrahydroindole (**7**), which is incapable of cyclization to 3-iminopyrrolizine, is observed (Scheme 5), the starting indole **7** being recovered unchanged.



Scheme 5.

Meanwhile, pyrrolizines **4a–d** can undergo the reversible ring opening to ethenylpyrroles **1a–d**,[5b] hence the parallel direct ethylthio for hydroxide nucleophilic substitution is not ruled out. To verify this assumption, we have studied *N*-methyl-2-(2-cyano-1-ethylthioethenyl)pyrroles **8a–d** in this reaction, which are incapable of cyclization to the pyrrolizines.

Indeed, the experiments have shown that under the same conditions in these pyrroles, the expected ethylthio–hydroxyl exchange does take place to give the corresponding enols **9a–d** in 50–85% yield (Scheme 6).



Pyrrole	R^1	R^2	X
9a	H	H	CN
9b	H	H	$CONH_2$
9c	$(CH_2)_4$		CN
9d	$(CH_2)_4$		$CONH_2$

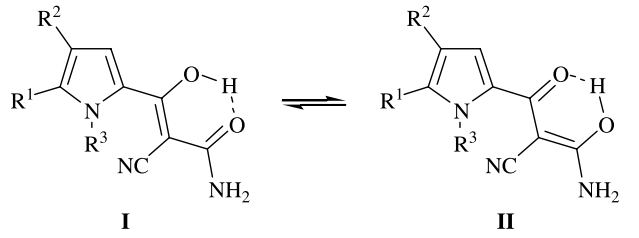
Scheme 6.

Thus, the ethylthio–hydroxyl exchange in 2-cyano-1-ethylthioethenylpyrroles **1a–d** probably proceeds along two competing routes: via 1-ethylthio-3-iminopyrrolizines **4a–d** (Scheme 3) and through the direct vinylic substitution (Scheme 6).

The stability of the tetrahydroindole **7** towards the substitution (Scheme 5) is likely to be associated with a higher electron-donating power of the tetrahydroindol-3-yl substituent compared to that of pyrrol-2-yl and steric hindrance from the 2-methyl and 4-methylene hydrogens.

A structural feature of 2-(2-carbamoyl-2-cyano-1-hydroxyethenyl)pyrroles **3a–d**, **9b**,**d** is a strong intramolecular hydrogen bond between the hydroxyl and carbonyl group showing up in the ^{1}H NMR spectra as a strong downfield-shifted signal of OH hydrogen ($CDCl_3$, 16.4–17.07 ppm).

In the ^{13}C NMR spectra of compounds **3a–d**, **9b**,**d**, the C-2 signal appears in the 66.9–69.7 ppm region, whereas that of C-1 is located at 173.0–178.0 ppm. Such positions of the signals indicate the oxygen atoms to be involved into conjugation with the double bond[12] and there is likely a tautomerism in solution[6a] (Scheme 7).



Scheme 7.

X-ray analysis of monocrystal **9b** shows that in the solid-state it exists solely in the enol form actually stabilized by intramolecular hydrogen bonding. The crystal structure consists of two crystallographically independent molecules, **A** and **B** (Fig. 1), which share same positions.

The OH hydrogen is located between two oxygen atoms at distances of 1.12 and 1.35 Å [these are average values calculated using O–H bond lengths and distances of H···O of both molecules (see Table 1)]. The hexagon O(1)C(6)C(7)C(8)O(2)H(1) has an almost flat conformation: maximum atom deflections are 0.02 and 0.03 Å for O(1A) and C(8B), respectively. Dihedral angles between the planes of the five-membered ring N(1)C(2)C(3)C(4)C(5) and hexagon O(1)C(6)C(7)C(8)O(2)H(1) are 1.2 and 4.2° for molecules **A** and **B**, respectively. Maximum atom deflections from the five-membered ring planes are 0.003 Å [atoms C(3A) and C(3B)]. Dihedral angles between the planes of hexagons and the corresponding substituents N(3)C(9)C(7) are 3.3 and 4.5° for molecules **A** and **B**, correspondingly. The N(2A) and N(2B) atom deflections from corresponding hexagon planes are 0.03 and 0.09 Å.

The length of intramolecular H-bond OH···O=C (1.35 Å) is close to that of the covalent bond O–H (1.12 Å). This, together with the C(6A)–C(7A) double bond elongation (1.393 Å) and C(7A)–C(8A) single bond shortening (1.453 Å), as well as with the flat structure of H-bound ring indicates the remarkably strong H-bonding in this case and significant contribution of the tautomer **II** (Scheme 7). The strength of the H-bond formed and the energy gain from the H-ring closure are likely to be the driving force of the unusually easy nucleophilic substitution of hydroxyl for alkylthio group.

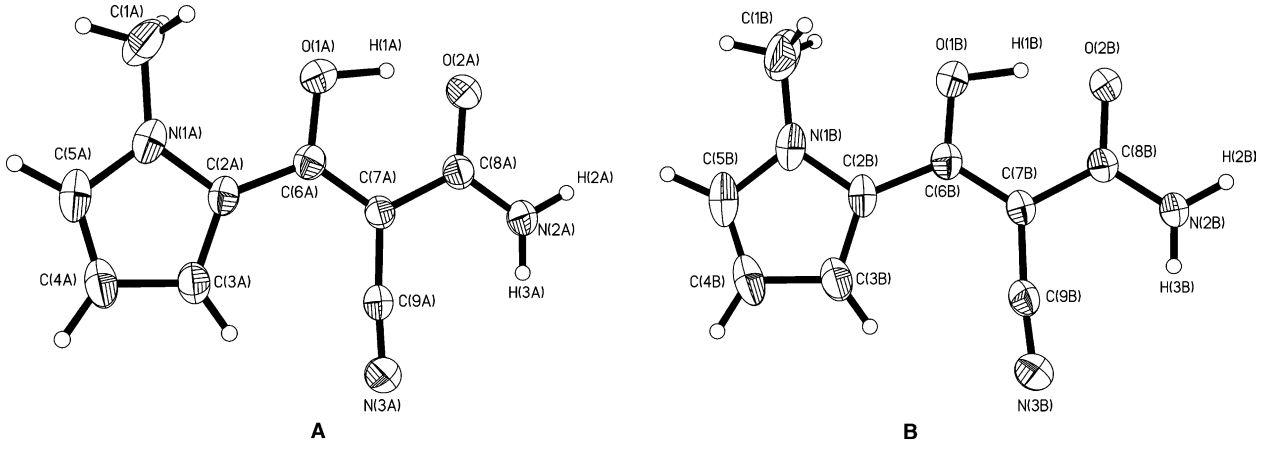


Figure 1. Labelling of atoms in the molecules of **9b**.

Table 1. Parameters of X–H···Y bonds

Contact type	*d*(X–H) (Å)	*d*(H···Y) (Å)	*D*(X···Y) (Å)	∠X–H···Y (°)
N(2AA)–H(2AA)···O(2AB)[a]	0.90(2)	2.14(2)	3.019(2)	165.9
N(2BB)–H(3BB)···N(3AB)[a]	0.88(1)	2.28(1)	3.038(2)	144.8
O(1AA)–H(1AA)···O(2AA)	1.13(2)	1.34(2)	2.435(1)	160.5
O(1BB)–H(1BB)···O(2BB)	1.10(2)	1.36(2)	2.429(1)	162.8

[a] Symmetry operation 1−x, −y, −z.

In conclusion, mild reaction conditions, availability of the starting materials and possibility of varying their structure, good preparative yields and high selectivity make our methods suitable for the synthesis of a new family of stable enols, 2-(2-cyano-1-hydroxyethenyl)pyrroles, rewarding models for basic study of reactivity.

3. Experimental

3.1. General methods

IR spectra of compounds synthesized (400–4000 cm^{-1}) were recorded in KBr pellets on a Bruker IFS-25 spectrometer. ^1H and ^{13}C NMR spectra were taken on a Bruker DPX 250 [250.13 (^1H) and 62.9 (^{13}C) MHz, respectively] and Bruker DPX 400 [400.13 (^1H) MHz] spectrometers using DMSO-d_6 as a solvent and HMDS as an internal reference. Structures of products were determined using 2D ^1H and ^{13}C NMR spectral techniques. ^{13}C resonance assignment was done with the use of 2D HSQC[13] and HMBC[14] heteronuclear correlation methods.

2D HMBC pulse sequence spectra were recorded using delays optimized for the direct $^1J(H,C)=145$ Hz and far $^nJ(H,C)=5$ Hz coupling constants.

Analyses of reaction mixtures and purity control of the compounds obtained were done using TLC on Silufol UV-254 plates with 10:1 diethyl ether/ethanol mixture as an eluent.

The starting 2-(2-cyano-1-ethylthioethenyl)pyrroles including previously unknown **8a–d** were synthesized from pyrrole-2-carbodithioates according to a published procedure.[10]

The X-ray study was performed at room temperature on an Enraf-Nonius CAD-4 ($\omega/2\theta$ scanning, Mo K_α emission, graphite monochromator). Crystalline structure was obtained by direct methods and subsequent Fourier syntheses using SHELXS-97 software.[15] The structure was fine-tuned using least-square technique in anisotropic full-matrix approximation for all non-hydrogen atoms in SHELXL-97 software.[15] Coordinates of hydrogen atoms were determined experimentally and improved in isotropic approximation.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 277477. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; (fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).

3.2. Synthesis of 2-(2-cyano-1-ethylthioethenyl)-1-methylpyrroles

3.2.1. 2-(2,2-Dicyano-1-ethylthioethenyl)-1-methylpyrrole (8a). To a stirred (0.5 h) suspension of malononitrile (0.59 g, 9 mmol) and KOH (0.50 g, 9 mmol) in 30 mL of DMSO, methyl 1-methyl-2-pyrrolecarbodithioate[16] (1.03 g, 6 mmol) was added. The reaction mixture was heated at 110 °C for 1.5 h, cooled to room temperature, then ethyl iodide (0.94 g, 6 mmol) was added. After stirring for 2 h, the mixture was diluted with brine (100 mL) and extracted with diethyl ether. After removal of ether, the residue was recrystallized from ethanol to afford 1.11 g (85%) of pyrrole **8a**, yellow solid, mp 68 °C. [Found: C, 60.75; H, 4.89; N, 19.45; S, 14.80. $C_{11}H_{11}N_3S$ requires C, 60.80; H, 5.00; N, 19.34; S, 14.76%]; ν_{max} (KBr): 2217, 1533, 1481, 1472, 1454, 1402, 1374, 1306, 1267, 1246, 1054, 945, 750, 688, 605 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.00 (dd, $^3J=2.6$ Hz, $^4J=1.7$ Hz, 1H, 5-H), 6.69 (dd, $^3J=3.9$ Hz, $^4J=1.7$ Hz, 1H, 3-H), 6.30 (dd, $^3J=3.9$, 2.6 Hz, 1H, 4-H), 3.75 (s, 3H, NMe), 2.79 (q, $^3J=7.3$ Hz, 2H, SCH_2), 1.22 (t, $^3J=7.3$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 168.6 (=*C*-SEt), 131.8 (5-C), 125.2 (2-C), 118.9 (3-C), 114.0 (CN), 113.4 (CN), 110.8 (4-C), 76.3 [=*C*$(CN)_2$], 35.4 (NMe), 29.7 (SCH_2), 14.4 (SCH_2*Me*).

3.2.2. 2-(2-Carbamoyl-2-cyano-1-ethylthioethenyl)-1-methylpyrrole (8b). To a stirred (0.5 h, room temperature) suspension of cyanoacetamide (0.76 g, 9 mmol) and KOH (0.50 g, 9 mmol) in 30 mL of DMSO, methyl 1-methyl-2-pyrrolecarbodithioate (1.03 g, 6 mmol) was added. The reaction mixture was heated at 110 °C for 1.5 h and cooled to room temperature. Ethyl iodide (0.94 g, 6 mmol) was added and stirring was continued for 2 h. The mixture was then diluted with brine (100 mL). Crystalline solid formed was filtered off, dried and recrystallized from ethanol to give 1.06 g (75%) of pyrrole **8b**, *E*/*Z* isomers, 1:5, yellow solid, mp 192 °C. [Found: C, 56.23; H, 5.63; N, 17.90; S, 13.53. $C_{11}H_{13}N_3OS$ requires C, 56.15; H, 5.57; N, 17.86; S, 13.63%]; ν_{max} (KBr): 3394, 3296, 3176, 2210, 1681, 1617, 1546, 1501, 1382, 1306, 1236, 939, 793, 732 cm^{-1}; (*E*)-isomer: ^1H NMR (400 MHz, DMSO-d_6): δ 6.90 (dd, $^3J=2.6$ Hz, $^4J=1.7$ Hz, 1H, 5-H), 6.42 (dd, $^3J=3.8$ Hz, $^4J=1.7$ Hz, 1H, 3-H), 6.28 (dd, $^3J=3.8$, 2.6 Hz, 1H, 4-H), 5.46 (br s, 2H, $CONH_2$), 3.55 (s, 3H, NMe), 2.70 (q, $^3J=7.5$ Hz, 2H, SCH_2), 1.17 (t, $^3J=7.5$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.8 (*C*=O), 161.3 (=*C*SEt), 128.4 (5-C), 124.5 (2-C), 116.7 (CN), 114.7 (3-C), 112.1 (4-C), 102.5 [=*C*(CN)$CONH_2$], 34.5 (NMe), 28.5 (SCH_2), 14.6 (SCH_2*Me*); (*Z*)-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (dd, $^3J=2.7$ Hz, $^4J=1.7$ Hz, 1H, 5-H), 6.29 (dd, $^3J=3.8$ Hz, $^4J=1.7$ Hz, 1H, 3-H), 6.23 (dd, $^3J=3.8$, 2.7 Hz, 1H, 4-H), 6.17 (br s, 1H, $CONH_2$), 5.65 (br s, 1H, $CONH_2$), 3.61 (s, 3H, NMe), 2.38 (q, $^3J=7.5$ Hz, 2H, SCH_2), 1.13 (t, $^3J=7.5$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 168.4 (=*C*SEt), 163.9 (*C*=O), 126.0 (2-C), 125.6 (5-C), 117.3 (CN), 112.1 (3-C), 109.0 (4-C), 101.7 [=*C*(CN)$CONH_2$], 34.2 (NMe), 28.1 (SCH_2), 13.6 (SCH_2*Me*).

3.2.3. 2-(2,2-Dicyano-1-ethylthioethenyl)-1-methyl-4,5,6,7-tetrahydroindole (8c). To a stirred (0.5 h, room temperature) suspension of malononitrile (0.59 g, 9 mmol) and KOH (0.50 g, 9 mmol) in 30 mL of DMSO, methyl 1-methyl-4,5,6,7-tetrahydroindole-2-carbodithioate, prepared according to[16] (1.35 g, 6 mmol) was added. The reaction mixture was heated at 110 °C for 1.5 h and cooled to room temperature. Ethyl iodide (0.94 g, 6 mmol) was added and stirring was continued for 2 h. The mixture was then diluted with brine (100 mL) and extracted with ether. After removal of ether, the residue was recrystallized from ethanol to give 1.27 g (78%) of tetrahydroindole **8c**, yellow

solid, mp 104–105 °C. [Found: C, 66.21; H, 6.44; N, 15.60; S, 11.79. $C_{15}H_{17}N_3S$ requires C, 66.39; H, 6.31; N, 15.48; S, 11.81%]; ν_{max} (KBr): 2209, 1491, 1448, 1380, 1356, 1306, 1267, 1221, 1171, 1086, 955, 816, 736, 639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.64 (s, 1H, 3-H), 3.62 (s, 3H, NMe), 2.95 (q, $^3J=7.3$ Hz, 2H, SCH_2), 2.65 (m, 2H, 7-CH_2), 2.55 (m, 2H, 4-CH_2), 1.88 (m, 2H, 5-CH_2), 1.78 (m, 2H, 6-CH_2), 1.28 (t, $^3J=7.3$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.9 (=*C*-SEt), 142.7 (5-C), 125.6 (2-C), 122.0 (4-C), 119.6 (3-C), 115.4 (CN), 114.6 (CN), 71.7 [=*C*$(CN)_2$], 32.3 (NMe), 30.2 (SCH_2), 23.0 (7-CH_2), 22.9 (5-CH_2), 22.8 (6-CH_2), 22.6 (4-CH_2), 14.4 (SCH_2*Me*).

3.2.4. 2-(2-Carbamoyl-2-cyano-1-ethylthioethenyl)-1-methyl-4,5,6,7-tetrahydroindole (8d). To a stirred (0.5 h, room temperature) suspension of cyanoacetamide (0.76 g, 9 mmol) and KOH (0.50 g, 9 mmol) in 30 mL of DMSO, methyl 2-(1-methyl-4,5,6,7-tetrahydroindole)-carbodithioate (1.16 g, 6 mmol) was added. The reaction mixture was heated at 110 °C for 1.5 h and cooled to room temperature. Ethyl iodide (0.94 g, 6 mmol) was added and stirring was continued for 2 h. The mixture was then diluted with brine (100 mL). Crystalline solid formed was filtered off, dried and recrystallized from ethanol to give 1.46 g (84%) of pyrrole **8d**, *E*/*Z* isomers, 1:5, yellow solid, mp 183–184 °C. [Found: C, 62.14; H, 6.88; N, 14.46; S, 11.28. $C_{15}H_{19}N_3OS$ requires C, 62.26; H, 6.62; N, 14.52; S, 11.08%]; ν_{max} (KBr): 3403–3180, 2206, 1688, 1655, 1589, 1512, 1380, 1077, 942, 921, 617 cm^{-1}; (*E*)-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 6.45 (s, 1H, 3-H), 5.35 (br s, 2H, $CONH_2$), 3.40 (s, 3H, NMe), 2.90 (q, $^3J=7.5$ Hz, 2H, SCH_2), 2.61 (m, 2H, 7-CH_2), 2.55 (m, 2H, 4-CH_2), 1.90 (m, 2H, 5-CH_2), 1.78 (m, 2H, 6-CH_2), 1.17 (t, $^3J=7.5$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.0 (*C*=O), 160.0 (=*C*SEt), 139.0 (5-C), 124.9 (2-C), 120.6 (4-C), 116.1 (3-C), 112.4 (CN), 98.2 [=*C*(CN)$CONH_2$], 30.8 (NMe), 29.4 (SCH_2), 23.0 (7-CH_2), 22.9 (5-CH_2), 22.8 (6-CH_2), 22.6 (4-CH_2), 14.4 (SCH_2*Me*); (*Z*)-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 6.19 (s, 1H, 3-H), 5.09 (br s, 2H, $CONH_2$), 3.48 (s, 3H, NMe), 2.50 (q, $^3J=7.5$ Hz, 2H, SCH_2), 2.61 (m, 2H, 7-CH_2), 2.55 (m, 2H, 4-CH_2), 1.90 (m, 2H, 5-CH_2), 1.78 (m, 2H, 6-CH_2), 1.13 (t, $^3J=7.5$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 167.4 (=*C*SEt), 164.4 (*C*=O), 134.4 (5-C), 124.9 (2-C), 118.9 (4-C), 112.4 (CN), 112.4 (3-C), 99.28 [=*C*(CN)$CONH_2$], 30.8 (NMe), 28.6 (SCH_2), 23.0 (7-CH_2), 22.9 (5-CH_2), 22.8 (6-CH_2), 22.6 (4-CH_2), 13.7 (Me).

3.3. Reaction of 2-(2-cyano-1-ethylthioethenyl)pyrroles 1a–d, 8a–d with NaOH/H_2O

General procedure for the synthesis of enols **3a–d**, **9a–d**. To a heated (45 °C) solution of pyrrole **1a–d** (0.5 mmol) in methanol (2 mL) a solution of NaOH (40 mg, 1 mmol) in water (1 mL) was added, and the mixture was stirred at the same temperature for 1 h. In the case of pyrrole **1c** 3-iminopyrrolizine **4c** is quantitatively precipitated after addition of alkali was isolated and characterised (it's ^1H NMR, IR spectra and mp were identical to those determined earlier[7b]).

Methanol was removed under vacuum, the residue was dissolved in H_2O (10 mL) and acidified with diluted HCl (up to pH 3). Crystalline solid formed was filtered off, washed with water and recrystallized from benzene.

3.3.1. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-4-ethyl-5-*n*-propylpyrrole (3a). Yield: 114 mg (92%); beige solid, mp 148–149 °C. [Found: C, 62.97; H, 7.18; N, 16.95. $C_{13}H_{17}N_3O_2$ requires C, 63.14; H, 6.93; N, 16.99%]; ν_{max} (KBr): 3483, 3298, 3190, 2200, 1654, 1602, 1559, 1478, 1442, 1362, 1336, 1319, 1284, 1209, 1144, 1003, 953, 833, 769, 720, 660, 527, 457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 16.45 (s, 1H, OH), 8.97 (br s, 1H, NH), 7.33 (d, $^4J=2.5$ Hz, 1H, 3-H), 5.92 (br s, 1H, $CONH_2$), 5.45 (br s, 1H, $CONH_2$), 2.58 (m, 2H, 1-CH_2 of propyl), 2.42 (q, $^3J=7.3$ Hz, 2H, CH_2 of ethyl), 1.64 (m, 2H, CH_2 of propyl), 1.16 (t, $^3J=7.3$ Hz, 3H, CH_3 of ethyl), 0.96 (t, $^3J=7.4$ Hz, 3H, CH_3 of propyl); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 174.2 ($CONH_2$ or=C–OH), 173.7 (=C–OH or $CONH_2$), 138.1 (5-C), 125.1 (4-C), 121.9 (2-C), 118.8 (CN), 116.7 (3-C), 66.9 [=*C*(CN)$CONH_2$], 27.0 (1-C of propyl), 22.9 (2-C of propyl), 18.3 (1-C of ethyl), 15.4 (Me of ethyl), 13.7 (Me of propyl).

3.3.2. 5-Butyl-2-(2-carbamoyl-2-cyano-1-hydroxyethenyl)-4-*n*-propylpyrrole (3b). Yield: 127 mg (92%); orange solid, mp 154–155 °C. [Found: C, 65.33; H, 7.70; N, 15.40. $C_{15}H_{21}N_3O_2$ requires C, 65.43; H, 7.69; N, 15.26%]; ν_{max} (KBr): 3446, 3416, 3344, 3195, 2198, 1660, 1604, 1555, 1473, 1441, 1366, 1141, 1000, 828, 776, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 16.43 (s, 1H, OH), 8.93 (br s, 1H, NH), 7.30 (d, $^4J=2.4$ Hz, 1H, H-3), 5.92 (br s, 1H, $CONH_2$), 5.43 (br s, 1H, $CONH_2$), 2.60 (m, 2H, 1-CH_2 of butyl), 2.36 (m, 2H, 1-CH_2 of propyl), 1.57 (m, 4H, 2-CH_2 of butyl and propyl), 1.37 (m, 2H, 3-CH_2 of butyl), 0.93 (m, 6H, CH_3 of butyl and propyl); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 174.2 ($CONH_2$ or =C–OH), 173.6 (=C–OH or $CONH_2$), 138.6 (5-C), 123.2 (4-C), 121.9 (2-C), 118.8 (CN), 117.3 (3-C), 66.9 [=*C*(CN)$CONH_2$], 31.8 (2-C of butyl), 27.3 (1-C of propyl), 24.8 (1-C of butyl), 23.9 (2-C of propyl), 21.9 (3-C of butyl), 13.8 (Me of propyl and butyl).

3.3.3. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-4,5,6,7-tetrahydroindole (3c). Yield: 109 mg (94%); dark orange solid, mp 203–204 °C. [Found: C, 61.94; H, 5.20; N, 17.85. $C_{12}H_{13}N_3O_2$ requires C, 62.3; H, 5.67; N, 18.17%]; ν_{max} (KBr): 3379, 3216, 2203, 1652, 1609, 1479, 1348, 1276, 1212, 1128, 828, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 16.43 (s, 1H, OH), 8.91 (br s, 1H, NH), 7.27 (d, $^4J=1.9$ Hz, 1H, H-3), 5.95 (br s, 1H, $CONH_2$), 5.42 (br s, 1H, $CONH_2$), 2.64 (m, 2H, 7-CH_2), 2.53 (m, 2H, 4-CH_2), 1.79 (m, 4H, 5,6-CH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 174.1 ($CONH_2$ or= C–OH), 173.9 (=C–OH or $CONH_2$), 136.5 (5-C), 120.3 (4-C), 122.5 (2-C), 118.7 (CN), 117.3 (3-C), 66.9 [=*C*(CN)$CONH_2$], 23.0 (7-CH_2), 22.6 (5-CH_2), 22.4 (6-CH_2), 22.4 (4-CH_2).

3.3.4. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-5-phenylpyrrole (3d). Yield: 109 mg (86%); dark yellow solid, mp 193–194 °C. [Found: C, 66.64; H, 4.59; N, 16.45. $C_{14}H_{11}N_3O_2$ requires C, 66.40; H, 4.38; N, 16.59%]; ν_{max} (KBr): 3469, 3441, 3334, 3276, 3205, 2203, 1652, 1593, 1559, 1469, 1455, 1295, 1072, 790, 756, 687 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 16.69 (s, 1H, OH), 9.47 (br s, 1H, NH), 7.59 (m, 3H, Ph-H_o, 3-H), 7.44 (m, 2H, Ph-H_m),

7.36 (m, 1H, Ph-H_p), 6.68 (m, 1H, 4-H), 6.02 (br s, 1H, $CONH_2$), 5.48 (br s, 1H, $CONH_2$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (br s, 1H, NH), 9.25 (br s, 1H, $CONH_2$), 7.77 (m, 2H, Ph-H_o), 7.32 (m, 2H, Ph-H_m), 7.16 (m, 1H, Ph-H_p), 7.00 (m, 1H, H-3), 6.49 (m, 1H, H-4), 6.00 (br s, 1H, $CONH_2$); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 174.8 ($CONH_2$ or =C–OH), 173.8 (=C–OH or $CONH_2$), 137.8 (5-C), 131.0 (Ph-C_i), 128.8 (Ph-C_m), 127.7 (Ph-C_p), 127.0 (CN), 125.5 (Ph-C_o), 109.1 (4-C), 119.3 (2-C), 117.0 (3-C), 69.1 [=*C*(CN)$CONH_2$].

3.3.5. 2-(2,2-Dicyano-1-hydroxyethenyl)-1-methylpyrrole (9a). Yield: 43 mg (50%); dark-pink solid, mp 114–115 °C ($CHCl_3$). [Found: C, 62.01; H, 4.77; N 24.08. $C_9H_7N_3O$ requires C, 62.42; H, 4.07; N, 24.26%]; ν_{max} (KBr): 3114, 2227, 2205, 1550, 1508, 1482, 1401, 1388, 1292, 1244, 1212, 1069, 892, 858, 760, 698 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.83 (dd, ^3J=2.4 Hz, ^4J=1.8 Hz, 1H, 5-H), 6.70 (dd, ^3J=3.8 Hz, ^4J=1.8 Hz, 1H, 3-H), 5.96 (dd, ^3J=3.8, 2.4 Hz, 1H, 4-H), 3.72 (s, 3H, NMe); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 178.5 (=C–OH), 129.2 (2-C), 127.0 (5-C), 122.3 (CN), 120.9 (CN), 113.7 (3-C), 106.3 (4-C), 47.7 [=*C*$(CN)_2$], 36.0 (NMe).

3.3.6. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-1-methylpyrrole (9b). Yield: 81 mg (85%); yellow solid, mp 161–162 °C (MeOH). [Found: C, 57.01; H, 4.97; N, 22.08. $C_9H_9N_3O_2$ requires C, 56.54; H, 4.74; N, 21.98%]; ν_{max} (KBr): 3410, 3347, 3286, 2200, 1667, 1603, 1559, 1532, 1466, 1407, 1353, 1236, 1158, 1108, 1070, 1024, 743, 669 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 18.38 (s, 1H, OH), 8.23 (br s, 1H, $CONH_2$), 7.23 (m, 1H, 3-H), 7.11 (m, 1H, 5-H), 6.19 (m, 1H, 4-H), 5.62 (br s, 1H, $CONH_2$), 3.83 (s, 3H, NMe); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 178.0 (=C–OH), 174.3 ($CONH_2$), 131.5 (5-C of pyrrole), 124.9 (CN), 118.6 (3-C), 118.4 (2-C), 108.4 (4-C), 69.7 [=*C*(CN)$CONH_2$], 37.5 (NMe). Crystal data for **9b** $C_9H_9N_3O_2$: M_w=191.19, a=11.859(2) Å, b=13.6319(2) Å, c=11.870(2) Å, α=90°, β=102.67(1), γ=90°, V=1872.1(5), D_{calcd}=1.36 g cm^{-3}, μ=0.100 mm^{-1}, Z=8, monoclinic, space group $P2_1/c$, λ=0.71073, 3028 total reflections, 2872 total independent reflections, 2347 total reflections with [$F_0>4\sigma(F_0)$], number of parameters 326, $(2\theta)_{max}$=47.94°, interval for h $-13\le h\le 13$, interval for k $0\le k\le 15$, interval for l $0\le l\le 13$, R-factor ($F_0>4\sigma(F_0)$) 0.030.

3.3.7. 2-(2-Dicyano-1-hydroxyethenyl)-1-methyl-4,5,6,7-tetrahydroindole (9c). Yield: 68 mg (60%); orange solid, mp 181–182 °C. [Found: C, 58.80; H, 5.56; N, 18.55. $C_{13}H_{13}N_3O$ requires C, 68.71; H, 5.77; N, 18.49%]; ν_{max} (KBr): 3140, 2223, 2205, 1533, 1514, 1468, 1456, 1409, 1253, 1223, 1200, 1100, 1073, 1028, 870, 810, 714 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.56 (s, 1H, 3-H), 3.47 (s, 3H, NMe), 2.49 (m, 2H, 7-CH_2), 2.35 (m, 2H, 4-CH_2), 1.70 (m, 2H, 6-CH_2), 1.59 (m, 2H, 5-CH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 175.4 (=C–OH), 137.2 (5-C), 124.0 (2-C), 118.2 (CN), 117.9 (4-C), 117.3 (CN), 115.6 (3-C), 52.8 [=*C*$(CN)_2$], 32.1 (NMe), 27.9 (7-CH_2), 22.5 (4-CH_2), 22.4 (6-CH_2), 21.6 (5-CH_2).

3.3.8. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-1-methyl-4,5,6,7-tetrahydroindole (9d). Yield: 103 mg (84%); orange solid, mp 191–192 °C (benzene). [Found: C, 63.56; H, 6.06; N, 16.90. $C_{13}H_{15}N_3O_2$ requires C, 63.66; H, 6.16; N, 17.13%]; ν_{max} (KBr): 3351, 3197, 2934, 2844, 2204, 1669, 1602, 1546, 1469, 1430, 1381, 1351, 1194, 1153, 1080, 1058, 985, 828, 810, 778, 707, 673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.92 (s, 1H, OH), 7.30 (s, 1H, 3-H), 5.99 (br s, 1H, $CONH_2$), 5.47 (br s, 1H, $CONH_2$), 3.69 (s, 3H, NMe), 2.56 (m, 2H, 7-CH_2), 2.50 (m, 2H, 4-CH_2), 1.84 (m, 2H, 6-CH_2), 1.71 (m, 2H, 5-CH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 177.2 (=C–OH or $CONH_2$), 174.5 ($CONH_2$ or =C–OH), 138.5 (5-C), 123.3 (2-C), 118.9 (CN), 118.5 (4-C), 116.8 (3-C), 68.5 [=*C*(CN)$CONH_2$].

3.4. Reaction of 1-(ethylthio)-3-imino-3*H*-pyrrolizines 4c, 6a,b with NaOH/H_2O

General procedure for the synthesis of enols **3c**, **5a**,**b**. To a heated (45 °C) solution (suspension in the case of 3-iminopyrrolisine **4c**) of 1-(ethylthio)-3-imino-3*H*-pyrrolizine (**6a** or **6b**) (0.5 mmol) in methanol (2 mL) a solution of NaOH (40 mg, 1 mmol) in water (1 mL) was added, and the mixture was stirred at the same temperature for 1 h. After the end of the reaction, methanol was removed under vacuum, the residue was dissolved in H_2O (10 mL), acidified with diluted HCl (up to pH 3). Crystalline solid formed was filtered off, washed with water and recrystallized from benzene.

3.4.1. 2-(2,2-Dicyano-1-hydroxyethenyl)-4-ethyl-5-*n*-propylpyrrole (5a). Yield: 89 mg (78%); yellow solid, mp 150–151 °C. [Found: C, 68.22; H, 6.57; N, 18.31. $C_{13}H_{15}N_3O$ requires C, 68.10; H, 6.59; N, 18.33%]; ν_{max} (KBr): 3280, 2233, 2214, 1580, 1526, 1481, 1205, 1158, 1009, 853, 837 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H, NH), 6.85 (d, ^4J=2.7 Hz, 1H, 3-H), 5.71 (br s, 1H, OH), 2.52 (m, 2H, CH_2 of propyl), 2.36 (q, ^3J=7.5 Hz, 2H, CH_2 of ethyl), 1.53 (m, 2H, CH_2 of propyl), 1.08 (t, ^3J=7.5 Hz, 3H, Me of ethyl), 0.86 (t, ^3J=7.0 Hz, 3H, Me of propyl); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 172.0 (=C–OH), 137.2 (5-C), 124.6 (4-C), 122.4 (2-C), 118.9 (CN), 117.6 (CN), 116.1 (3-C), 48.9 [=*C*$(CN)_2$], 27.1 (1-C of propyl), 22.8 (2-C of propyl), 18.3 (1-C of ethyl), 15.4 (Me of ethyl), 13.7 (Me of propyl).

3.4.2. 5-*n*-Butyl-2-(2,2-dicyano-1-hydroxyethenyl)-4-*n*-propylpyrrole (5b). Yield: 116 mg (90%); yellow crystals, mp 148–149°C. [Found: C, 69.80; H, 7.48; N, 16.10. $C_{15}H_{19}N_3O$ requires C, 70.01; H, 7.44; N, 16.33%]; ν_{max} (KBr): 3287, 2225, 2204, 1579, 1525, 1509, 1479, 1340, 1221, 1192, 1155, 1073, 861, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (br s, 1H, NH), 7.32 (m, 1H, 3-H), 2.61 (m, 2H, CH_2 of butyl), 2.36 (m, 2H, CH_2 of propyl), 1.56 (m, 4H, CH_2 of propyl and butyl), 1.36 (m, 2H, CH_2 of butyl), 0.93 (m, 6H, CH_3 of propyl and butyl); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.0 (=C–OH), 136.7 (5-C), 123.6 (2-C of pyrrole), 122.1 (4-C), 119.9 (CN), 118.6 (CN), 115.8 (3-C), 47.8 [=*C*$(CN)_2$], 31.8 (1-C of butyl), 27.3 (1-C of propyl), 24.8 (2-C of propyl), 23.9 (2-C of butyl), 21.9 (3-C of butyl), 13.80 (Me of butyl and propyl).

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