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The first chemoselective synthesis of functionalized 3-vinylpyrroles

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Abstract—3-(1-Alkylthio-2-cyano-2-X-ethenyl)pyrroles (X = CN, $CONH_2$, CO_2Et) have been synthesized in 28–58% yields by the reaction of pyrrole-3-carbodithioates with CH-acids (malononitrile, cyanoacetamide, cyanoacetate) in the KOH–DMSO system.

C-Vinylpyrroles are versatile building blocks for the design of complex heterocyclic assemblies with pyrrole structural units.[1,2] They are used in total syntheses of porphyrins, vitamin B_{12}, haemoglobin, chlorophylls and similar important compounds with life-supporting functions.[3] Of special interest are functionalized *C*-vinylpyrroles having a double bond polarized in a push–pull manner by substituents capable of further heterocyclization to form conjugated and fused heterocyclic compounds structurally close to natural pyrrole assemblies. Recently, functionalized *C*-vinylpyrroles have started to draw attention as molecular optical switches, including the ultra-fast ones used in construction of micro- and nano-opto-electronic devices,[4] as well as ligands for new photocatalysts and biologically active complexes.[5] Therefore, efforts in the further development of new synthetic routes to *C*-vinylpyrroles[6] might be rewarding.

Some 2-vinylpyrroles bearing functional substituents at the vinyl group were synthesized from 1-pyrrolylmagnesium bromide and 2-cyano-3-ethoxy-3-ethylthioacrylonitrile,[7] or from pyrrole-2-carbodithioates and tetracyanoethylene oxide,[8] or via condensation of pyrrole-2-carbodithioates with active methylene compounds.[9] Meanwhile, the corresponding 3-vinyl isomers remain inaccessible. To our knowledge, the only representative of 3-vinylpyrroles with a push–pull vinyl group, 1-tosyl-2-cyclohexyl-3-(1-nitro-2-cyclohexylethenyl)pyrrole, was isolated as a side product (12% yield) from the reaction products of 1,4-dicyclohexyl-2,3-dinitro-1,3-butadiene with tosylmethylisocyanide.[6b,10]

To explore a new approach to the synthesis of functionally substituted 3-vinylpyrroles we have investigated the condensation of pyrrole-3-carbodithioates **1**–**3** (available recently[11]) with CH-acids using as typical representatives: malononitrile, cyanoacetamide and cyanoacetate. The results were far from predictable, since according to quantum chemical calculations (MP2/6+G**),[12] pyrrole-3-carbodithioates are 10–13 kcal/mol less stable than their 2-isomers.

In spite of this fact, we have found that functionalized 3-vinylpyrroles **5a**–**f** can be synthesized (in 28–58% yields, unoptimized) on heating (100–110°C, 1.5 h) pyrrole-3-carbodithioates **1**–**3** with the above-mentioned CH-acid anions generated in KOH–DMSO (room temperature, 0.5 h) followed by in situ alkylation of the intermediate thiolates **4** at room temperature[13] (Scheme 1).

Decreased yields of 3-vinylpyrroles **5a**–**f** as compared to those of the 2-isomers[9] can be explained by the lower stability of pyrrole-3-carbodithioates (relative to pyrrole-2-carbodithioates) as mentioned above: desulfurized pyrroles **6a**–**f** are always present (in amounts up to 10–20%) among the reaction products, along with unreacted pyrrole-3-carbodithioates **1**–**3**. Steric hindrance and the lower electrophilicity of the carbodi-

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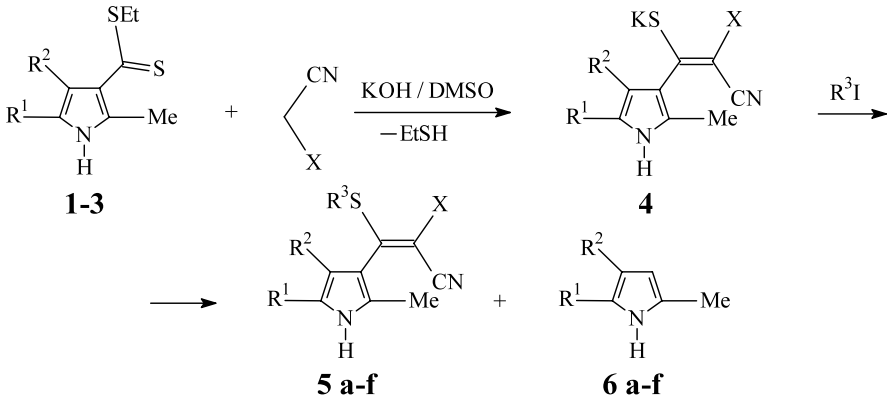


5	R^1	R^2	R^3	X	Yield, %	Mp., °C
a	Me	Me	Et	CN	58	100
b	$(CH_2)_4$		Me	CN	37	190
c	$(CH_2)_4$		Et	CN	41	153
d	Ph	H	Et	CN	28	145
e	Ph	H	Et	$CONH_2$	38	100
f	Ph	H	Et	CO_2Et	30	132

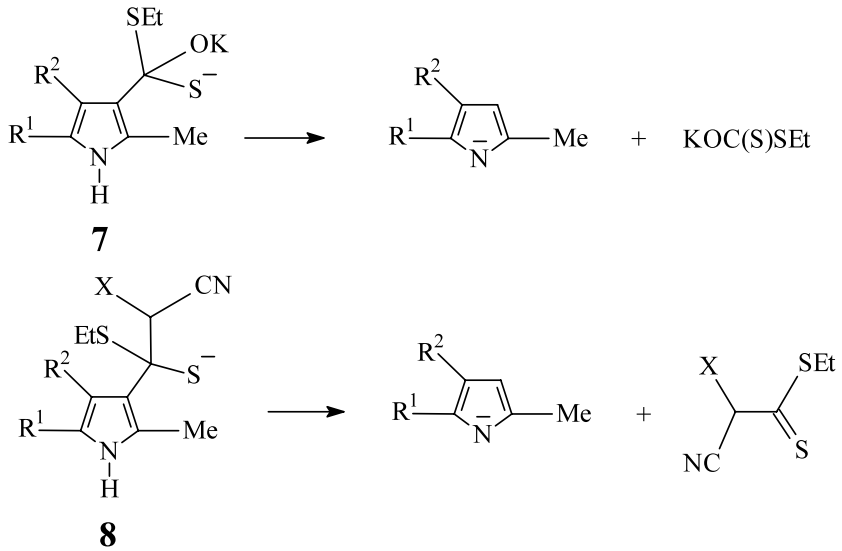
Scheme 1.

thioate function at position 3 may also contribute to the decreased yield. The pyrroles **6a–f** may be the elimination products from the intermediates **7** or **8** (Scheme 2).

Unlike the synthesis of the 2-vinyl isomers,[9] the condensation studied is chemoselective, because in this case no intramolecular cyclization with participation of the NH-function is possible. The reaction of the ethyl 2-methyl-5-phenylpyrrole-3-carbodithioate with the CH-acids is stereoselective: the 3-vinylpyrroles **5e–f** are always formed as a single isomer, probably having the less sterically hindered *E*-configuration with the *syn*-orientation of the pyrrole and CN groups.

3-Vinylpyrroles **5a–f** are brightly colored (yellow or orange) crystals. In their IR spectra the NH stretching of the pyrrole ring appears in the 3209–3381 cm^{-1} region. In the same region (3210–3450 cm^{-1}) of pyrrole **5e** there are amide NH bands (symmetric and asymmetric vibrations). The nitrile group for all the pyrroles **5a–f** is observed as a single band at 2192–2220 cm^{-1}. The shapes and intensities of the ^1H NMR signals are in agreement with the structures of 3-vinylpyrroles **5a–f**.

Thus, a new general synthesis of inaccessible 3-vinylpyrroles with exhaustively functionalized double bonds has been developed based on the condensation of pyrrole-3-carbodithioates with CH-acids. Since the



Scheme 2.

starting 2,5-disubstituted pyrroles[14] and their corresponding pyrrole-3-carbodithioates[11] have recently become available and the selection of CH-acids is practically unlimited, the scope and utility of this synthesis promises much.

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References

1. (a) Burns, D. H.; Smith, K. M. *J. Chem. Res. (S)* **1990**, *6*, 178; (b) Murase, M.; Yoshida, S.; Hosaka, T.; Tobinaga, S. *Chem. Pharm. Bull.* **1991**, *39*, 489; (c) Selim, M. A. *Aswan Sci. Technol. Bull.* **1992**, *13*, 60; (d) Xiao, D.; Ketcha, D. M. *J. Heterocyclic Chem.* **1995**, *32*, 499.
2. (a) Bakhshi, A. K.; Lovleen, A. *Superlattices Microstruct.* **1993**, *13*, 437; (b) Berlin, A.; Canavesi, A.; Pagani, G.; Schiavon, G.; Zecchin, S.; Zotti, G. *Synth. Met.* **1997**, *84*, 451; (c) Entezami, A.; Rahmatpour, A. *Eur. Polym. J.* **1998**, *34*, 871; (d) Kim, I. T.; Elsenbaumer, R. L. *Macromolecules* **2000**, *33*, 6407.
3. (a) Gossauer, A. *Die chemie der Pyrrole*; Springer-Verlag: Berlin-Heidelberg-New York, 1974; (b) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: New York, 1989.
4. (a) Hayes, R. T.; Wasielewski, M. R.; Gosztola, D. *J. Am. Chem. Soc.* **2000**, *122*, 5563; (b) Harmjanz, M.; Gill, H. S.; Scott, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 10476; (c) Rurack, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 385.
5. Sour, A.; Boillot, M.-L.; Riviere, E.; Lesot, P. *Eur. J. Inorg. Chem.* **1999**, *12*, 2117.
6. (a) Trofimov, B. A. *The Chemistry of Heterocyclic Compounds. Pyrroles*; Wiley: New York, 1992; Vol. 48; (b) Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I.; Trofimov, B. A. *Usp. Khim.* **2002**, *71*, 641. See also *Russ. Chem. Rev.* **2002**, *71*, 563.
7. Hartke, K.; Radau, S. *Liebigs Ann. Chem.* **1974**, 2110.
8. Tominaga, Y.; Matsuoka, Y.; Oniyama, Y.; Uchimura, Y.; Komiya, H.; Hirayama, M.; Kohra, S.; Hosomi, A. *J. Heterocyclic Chem.* **1990**, *27*, 647.
9. Sobenina, L. N.; Mikhaleva, A. I.; Sergeeva, M. P.; Petrova, O. V.; Aksamentova, T. N.; Kozyreva, O. B.; Toryashinova, D. S. D.; Trofimov, B. A. *Tetrahedron* **1995**, *51*, 4223.
10. Dell'Erba, C.; Giglio, A.; Mugnoli, A.; Novi, M.; Petrillo, G.; Stagnaro, P. *Tetrahedron* **1995**, *51*, 5181.
11. Trofimov, B. A.; Sobenina, L. N.; Mikhaleva, A. I.; Demenev, A. P.; Tarasova, O. A.; Ushakov, I. A.; Zinchenko, S. V. *Tetrahedron* **2000**, *56*, 7325.
12. Trofimov, B. A.; Vitkovskaya, N. M.; Kobychev, V. B.; Larionova, E. Y.; Sobenina, L. N.; Mikhaleva, A. I.; Demenev, A. P. *Sulfur Lett.* **2001**, *24*, 181.
13. **Typical procedure**: A mixture of a CH-acid (3 mmol), KOH (3 mmol) and DMSO (10 ml) was stirred for 0.5 h at room temperature, a pyrrolecarbodithioate (2 mmol) was added and the reaction mixture was heated at 110°C for 1.5 h, then cooled to room temperature and an alkyl halide (2 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and diluted with brine (30 ml). The precipitated crystals were filtered off, washed with water, dried, and finally purified chromatographically (column with Al_2O_3, eluent–hexane). If crystals did not form, the resultant solution was extracted with diethyl ether, and the residue, after removal of the ether, was purified by column chromatography.
3-(2,2-Dicyano-1-ethylthioethenyl)-2,4,5-trimethylpyrrole 5a. ^{1}H NMR ($CDCl_3$): δ 8.14 (br. s, 1H, NH), 2.70 (q, 2H, $J=7.4$ Hz, SCH_2), 2.22 (s, 3H, Me^2), 2.09 (s, 3H, Me^4), 1.95 (s, 3H, Me^5), 1.13 (t, 3H, $J=7.4$ Hz, Me). $C_{13}H_{15}N_3S$ (245.34): calcd C, 63.64; H, 6.16; N, 17.13; S, 13.07. Found: C, 63.40; H, 6.33; N, 16.96; S, 13.50.
3-(2,2-Dicyano-1-methylthioethenyl)-2-methyl-4,5,6,7-tetrahydroindole 5b. ^{1}H NMR ($CDCl_3$): δ 8.00 (br. s, 1H, NH), 2.38 (m, 4H, $CH_2^{4,7}$), 2.27 (s, 6H, Me), 1.77 (m, 4H, $CH_2^{5,6}$). $C_{14}H_{15}N_3S$ (257.36): calcd C, 65.34; H, 5.87; N, 16.33; S, 12.46. Found: C, 65.00; H, 6.39; N, 16.41; S, 12.07.
3-(2,2-Dicyano-1-ethylthioethenyl)-2-methyl-4,5,6,7-tetrahydroindole 5c. ^{1}H NMR ($CDCl_3$): δ 8.13 (br. s, 1H, NH), 2.76 (q, 2H, $J=7.4$ Hz, SCH_2), 2.49 (m, 2H, CH_2^7), 2.41 (m, 2H, CH_2^4), 2.27 (s, 3H, Me^2), 1.75 (m, 4H, $CH_2^{5,6}$), 1.14 (t, 3H, $J=7.4$ Hz, Me): $C_{15}H_{17}N_3S$ (271.38) calcd for: C, 66.39; H, 6.31; N, 15.48; S, 11.82. Found: C, 66.64; H, 6.29; N, 15.53; S, 12.07.
3-(2,2-Dicyano-1-ethylthioethenyl)-2-methyl-5-phenylpyrrole 5d. ^{1}H NMR ($CDCl_3$): δ 9.20 (br. s, 1H, NH), 7.45, 7.37, 7.25 (m, 5H, Ph), 6.46 (d, 1H, $J=2.9$ Hz, H^4), 2.92 (q, 2H, $J=7.4$ Hz, SCH_2), 2.40 (s, 3H, Me^2), 1.18 (t, 3H, $J=7.4$ Hz, Me). $C_{17}H_{15}N_3S$ (293.39): calcd C, 69.59; H, 5.15; N, 14.32; S, 10.93. Found: C, 69.20; H, 5.29; N, 14.58; S, 11.28.
3-(2-Carbamoyl-2-cyano-1-ethylthioethenyl)-2-methyl-5-phenylpyrrole 5e. ^{1}H NMR ($CDCl_3$): δ 8.57 (br. s, 1H, NH), 7.44, 7.36, 7.25 (m, 5H, Ph), 6.33 (d, 1H, $J=2.8$ Hz, H^4), 6.13 (br. s, 1H, $CONH_2$), 5.63 (br. s 1H, $CONH_2$), 2.62 (q, 2H, $J=7.4$ Hz, SCH_2), 2.32 (s, 3H, Me^2), 1.12 (t, 3H, $J=7.4$ Hz, Me). $C_{17}H_{17}N_3OS$ (311.40): calcd C, 65.57; H, 5.50; N, 13.49; S, 10.30. Found: C, 65.23; H, 5.23; N, 13.80; S, 10.78.
3-(2-Carbethoxy-2-cyano-1-ethylthioethenyl)-2-methyl-5-phenylpyrrole 5f. ^{1}H NMR ($CDCl_3$): δ 8.40 (br. s, 1H, NH), 7.38, 7.30, 7.18 (m, 5H, Ph), 6.26 (d, 1H, $J=2.9$ Hz, H^4), 4.32 (q, 2H, $J=7.1$ Hz, CH_2CO_2), 2.64 (q, 2H, $J=7.4$ Hz, SCH_2), 2.28 (s, 3H, Me^2), 1.37 (t, 3H, $J=7.4$ Hz, Me), 1.11 (t, 3H, $J=7.4$ Hz, Me). $C_{19}H_{20}N_2O_2S$ (340.44): calcd C, 67.03; H, 5.92; N, 8.23; S, 9.40. Found: C, 67.43; H, 5.60; N, 8.41; S, 9.73.
14. Trofimov, B. A.; Tarasova, O. A.; Mikhaleva, A. I.; Kalinina, N. A.; Sinegovskaya, L. M.; Henkelman, J. *Synthesis* **2000**, *11*, 1585.