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Reaction of Pyrrole Anions with Carbon Disulfide. Synthesis of Pyrrole-3-carbodithioates

Boris A. Trofimov,[a,*] Lubov' N. Sobenina,[a] Al'bina I. Mikhaleva,[a] Andrey P. Demenev,[a] Ol'ga A. Tarasova,[a] Igor' A. Ushakov[b] and Sergey V. Zinchenko[a]

[a]*A.E. Favorsky Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Russ-664033 Irkutsk, 1 Favorsky, Russia*
[b]*Irkutsk State Polytechnic University, Russ-664074, Irkutsk, 83 Lermontov, Russia*

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Abstract—2,5-Disubstituted pyrroles react with carbon disulfide in the system KOH–DMSO with selective formation of pyrrole-3-carbodithioate anions from which pyrrole-3-carbodithioates were prepared by ethylation in 36–61% yield. From 2-methyl-5-phenyl(2-furyl- or 2-thienyl)pyrroles only pyrrole-3-carbodithioates are formed, with no isomeric pyrrole-4-carbodithioates being present. The reaction direction depends on pyrrole ring substitution: unsubstituted pyrrole selectively forms pyrrole-1-carbodithioate, whereas 2-methyl-, 2,3- and 2,4-dimethylpyrroles give exclusively pyrrole-2-carbodithioates under the same conditions.

Pyrroledithiocarboxylic acids and their derivatives are related to a poorly understood class of synthetically and biologically attractive pyrrole compounds, in particular, as highly potent starting materials for constructing complex pyrrole systems. Prior to our research in this field[1,2] only pyrrole-1-carbodithioates obtained by addition of pyrroles to carbon disulfide in the presence of superbases were known.[3] The only described representative of pyrrole-2-carbodithioates, ethyl pyrrole-2-dithiocarboxylate, was synthesized via *N*-pyrrolylmagnesium bromide.[4] The synthesis of a salt of 4,5-dimethyl-2-pyrroledithiocarboxylic acid from the corresponding pyrrole and carbon disulfide in an aqueous-alkaline medium (89% yield)[5] proved to be irreproducible.[1]

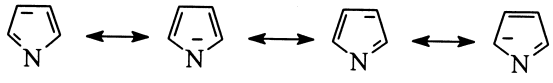
It turned out that in the superbase system KOH–DMSO, pyrroles regioselectively add to carbon disulfide at the position 2 to form pyrrole-2-carbodithioates; the only exception is unsubstituted pyrrole, which reacts as before at position 1 only, and 2-arylpyrroles affording some amount (24–29%) of pyrrole-1-carbodithioates along with the corresponding 2-isomers as major products (52–59%).[1,2]

In the literature there are no data concerning the synthesis of pyrrole-3-carbodithioates from pyrroles and carbon disulfide in the presence of superbases. It is known that in the presence of potassium metal 2,5-dimethylpyrrole in toluene selectively forms the corresponding pyrrole-1-carbodithioate with carbon disulfide.[6] This suggests that the pyrrole anion could react with carbon disulfide exclusively via the nitrogen atom on condition that the positions 2 and 5 are substituted. Meanwhile, judging by the pyrrole anion resonance structures, the electrophilic attack is quite possible to be directed to the 3 and 4 positions as well (Scheme 1). When the substituents are in positions 2 and 5, the attack by a carbon disulfide molecule at positions 3 and 4 becomes even more probable.

For the first time we managed to involve a series of 2,5-disubstituted pyrroles (**1a**–**f**) into the reaction with carbon disulfide in KOH–DMSO system. For comparison, 2-methyl-, 2,3- and 2,4-disubstituted pyrroles (**1g**–**j**) were studied under the same conditions.

Contrary to data[3,6] and our expectations, under the conditions examined, all the 2,5-disubstituted pyrroles react with carbon disulfide in a regio-selective manner to give ethyl pyrrole-3-carbodithioates (**3a**–**f**) in 36–61% yield after EtI-ethylation of the salts (**2a**–**f**) (Scheme 2).[7]

The reaction was carried out at room temperature over 3 h. The pyrrole–KOH–carbon disulfide molar ratio was 1:2:2. The intermediate salts were EtI ethylated without isolation (room temperature, 2 h). Under the same conditions the pyrroles (**1g**–**j**) without substituents in position 5 reacted



Scheme 1.

Keywords: pyrrole anions; carbon disulfide; pyrrole-3-carbodithioates; regioselectivity.

* Corresponding author. Fax: +7-39-60-46; e-mail: admin@irioch.irk.ru

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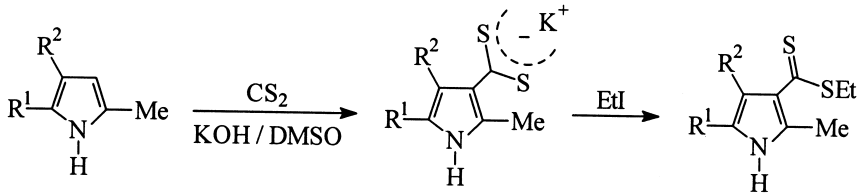


(1a-f) (2a-f) (3a-f)

1, 2, 3	R^1	R^2	Product	Yield (%)
a	Me	H	**3a**	52
b	Me	Me	**3b**	43
c	$(CH_2)_4$		**3c**	36
d	Ph	H	**3d**	61
e	2-Furyl	H	**3e**	44
f	2-Thienyl	H	**3f**	46

Scheme 2.

in the same manner to form ethyl pyrrole-2-carbodithioates (**3g**–**j**) in 46–62% yield (Scheme 3).

In no case we could fix formation of isomeric pyrrolecarbodithioates (all the reaction mixtures were analyzed by ^{1}H NMR spectroscopy prior to isolation of products on aluminum oxide). The reaction mixtures always contain diethyldisulfide (up to 12% per ethyl iodide taken) as a side product formed as the result of ethylation and oxidation of the products of carbon disulfide alkaline hydrolysis.

Comparing the results with those obtained previously for unsubstituted pyrrole, which gives only pyrrole-1-carbodithioate,[2,3] we come to an unexpected conclusion that the introduction of a single methyl substituent into the pyrrole ring position 2 is enough to change the direction of carbon disulfide attack on the multidentate pyrrole anion.

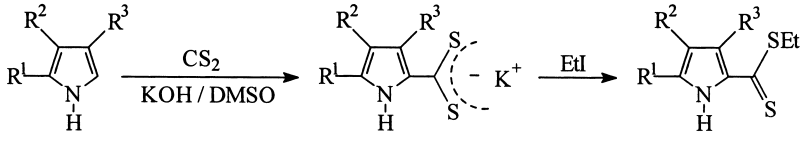
Earlier we have shown that 2-aryl- and 2-aryl-3-alkylpyrroles react with carbon disulfide under the same conditions to form a mixture of pyrrole-1- and pyrrole-2-carbodithioates.[1,2] However, the anions of 2-methyl-5-aryl-(hetaryl)pyrroles (**1d**–**f**) add to carbon disulfide selectively with the formation of only pyrrole-3-carbodithioates (**3d**–**f**): in the reaction mixture there are not even traces of either pyrrole-1- or, quite possible in this case, pyrrole-4-carbodithioates (**4d**–**f**) (Scheme 4).

The formation of isomers (**4d**–**f**) seems to be sterically hindered by either hydrogen atom in the phenyl radical *o*-position or lone electron pairs of heteroatoms (O, S). The choice between alternative structures—pyrrole-3- and pyrrole-4-carbodithioates for compounds (**3d**–**f**), was made on the basis of ^{1}H NMR data.

It should be noted that in contrast to pyrroles (**1a**–**d**), which react with carbon disulfide completely (no the pyrroles recovered), the conversion of pyrroles (**1e**) and (**1f**) is 81 and 79%, respectively.

Thus, the reaction of 2,5-substituted pyrroles with carbon disulfide in KOH–DMSO system is of general character. The reaction involves pyrroles with alkyl substituents as well as those annelated with saturated aliphatic rings or linked with aryl and hetaryl substituents. In all cases pyrrole-3-carbodithioates are selectively formed.

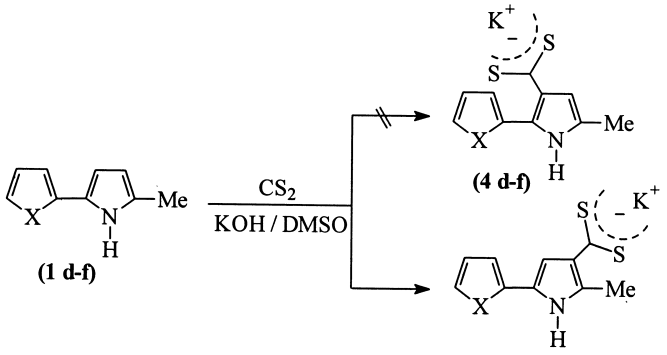
The structure of compounds is supported by elemental analysis, IR, ^{1}H and ^{13}C NMR spectroscopy. The IR spectra of the pyrroles (**3a**–**j**) are characterized by the presence of



(1g-j) (2g-j) (3g-j)

1, 2, 3	R^1	R^2	R^3	Product	Yield (%)
g	Me	H	H	**3g**	46
h	Me	Me	H	**3h**	51
i	Me	H	Me	**3i**	48
j	*t*-Bu	H	Me	**3j**	62

Scheme 3.



Scheme 4.

intense bands in the 3300–3400 cm^{-1} region, corresponding to the NH group vibrations. In the ^1H NMR spectra of all the pyrroles (**3a**–**j**) there are quartets (SCH_2) and triplets (Me) of the SEt group in the 3.40–3.32 and 1.40–1.34 ppm region, respectively. The pyrrole proton signals in compounds (**3a**, **d**–**h**) in the *ortho*-position to the C(S)SEt group are in the 7.04–6.48 ppm range. The pyrrole protons in compounds (**3g**, **i**, **j**) in the *meta*-position to the C(S)SEt group resonate in the 6.02–5.92 ppm range. These protons are characterized by a far spin–spin coupling (J_{NH-H-3}= 2.40–3.50 Hz) transmitted through a W-shaped fragment. The NH group protons in pyrrole-3-carbodithioates (**3a**–**f**) manifest themselves as a broad singlet in the 8.68–7.79 ppm region, whereas those in pyrrole-2-carbodithioates (**3g**–**j**) are observed in the 9.68–9.34 ppm range. The methyl group singlet in a position neighbouring to the C(S)SEt group in (**3a**–**f**, **i**, **j**) is shifted by 0.2–0.4 ppm downfield and observed in the 2.67–2.37 ppm range.

Dimeric homonuclear ^1H–^1H Noesy spectra of pyrroles (**3d**–**f**) point to interaction of the NH proton with methyl group and the H-4 proton with benzene and furan ring *ortho*-protons in compounds (**3d**) and (**3e**). This allows the C(S)SEt group position to be uniquely identified. The interaction of the NH proton with both the methyl group and the thiophene ring H-3 proton, which is observed for the pyrrole (**3f**), bears witness to the predominant *anti*-orientation of heterocycles in contrast the *syn*-orientation of furan analogue (**3e**). The absence of cross peak of methyl group with pyrrole ring proton H-3 provides further evidence for the presence of C(S)SEt group in this position (Scheme 5).

The structure of compound (**3f**) was also proved by ^{13}C NMR spectroscopy. The signals were assigned using dimeric heteronuclear techniques HSQC[8] and HMBC.[9] The methyl group proton cross peak through three bonds to a quaternary carbon in the pyrrole ring position 3 is indicative of the presence of carbodithioate group in the above position.

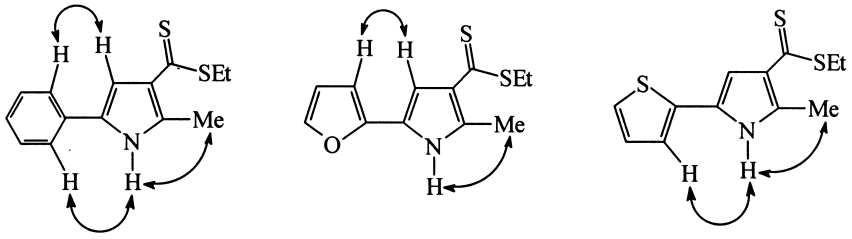
Mild conditions of dithiocarbonization, availability of the initial compounds and possibility of structural variations, good preparative yields and high selectivity of the reaction makes the developed synthesis of hardly accessible pyrrole-3-carbodithioates a rather promising process for broad application in the chemistry of pyrroles.

Experimental

IR Spectra were recorded on a Bruker IFS 25 instrument (KBr pellets). ^1H and ^{13}C NMR spectra were run on a Bruker DPX 400 spectrometer (250.13 and 101.61 MHz, respectively, HMDS, chloroform). Analysis of the reaction mixtures and purity control of the products were carried out by TLC on Silufole UV-254. The products were separated by column chromatography (Al_2O_3, hexane).

Synthesis of pyrrolecarbodithioates (3a–j) (routine procedure)

Pyrrole (10 mmol) and KOH (1.12 g, 20 mmol) are stirred for 0.5 h in 20 ml of DMSO, then carbon disulfide (1.52 g, 20 mmol) is added. The reaction mixture is allowed to stand 3 h at room temperature, after addition of ethyl iodide (1.56 g, 10 mmol) the resultant mixture is stirred for 2 h, diluted with water and extracted with ether. The residue is fractionated by column chromatography. The isolated products are diethyldisulfide (10–12% yield basing on



Scheme 5.

ethyl iodide), unreacted pyrrole (in the case of pyrroles (**3e**) and (**3f**)) and pyrrolecarbodithioates.

Ethyl 2,5-dimethylpyrrole-3-carbodithioate (3a). 52%, purity 95% (NMR date), yellow crystals, mp 60°C; [Found: C, 54.03; H, 6.34; N, 6.67; S, 31.71. $C_9H_{13}NS_2$ requires C, 54.23; H, 6.57; N, 7.03; S, 32.17%]; ν_{max}(KBr) 3266, 2964, 2921, 2869, 1595, 1502, 1449, 1416, 1367, 1327, 1242, 1192, 1126, 1017, 988, 826, 711, 678, 508 cm^{-1}; δ_H (250.13 MHz, $CDCl_3$) 8.17 (1H, br s, NH), 6.48 (1H, d, *J*=2.8 Hz, H-4), 3.33 (2H, q, *J*=7.4 Hz, SCH_2), 2.58 (3H, s, Me-2), 2.19 (3H, s, Me-5), 1.37 (3H, t, *J*=7.4 Hz, Me).

Ethyl 2,4,5-trimethylpyrrole-3-carbodithioate (3b). 43%, yellow crystals, mp 38°C; [Found: C, 56.64; H, 6.84; N, 7.11; S, 29.55. $C_{10}H_{15}NS_2$ requires C, 56.29; H, 7.09; N, 6.56; S, 30.06%]; ν_{max}(KBr) 3387, 2957, 2922, 2852, 1597, 1503, 1447, 1424, 1399, 1380, 1322, 1244, 1118, 1064, 1042, 996, 978, 965, 810, 774, 634, 577, 546 cm^{-1}; δ_H (250.13 MHz, $CDCl_3$) 7.88 (1H, br s, NH), 3.30 (2H, q, *J*=7.4 Hz, SCH_2), 2.37 (3H, s, Me-2), 2.14 (3H, s, Me-4), 2.04 (3H, s, Me-5), 1.35 (3H, t, *J*=7.4 Hz, Me).

Ethyl 2-methyl-4,5,6,7-tetrahydroindole-3-carbodithioate (3c). 36%, yellow crystals, mp 60°C; [Found: C, 59.85; H, 7.01; N, 5.31; S, 26.32. $C_{12}H_{17}NS_2$ requires C, 60.20; H, 7.16; N, 5.58; S, 26.79%]; ν_{max}(KBr), 3320, 2952, 2926, 2851, 1607, 1458, 1437, 1406, 1376, 1320, 1246, 1118, 1016, 990, 943, 890, 845, 776, 650 cm^{-1}; δ_H (250.13 MHz, $CDCl_3$) 7.79 (1H, br s, NH), 3.31 (2H, q, *J*=7.4 Hz, SCH_2), 2.77 (2H, m, CH_2-7), 2.49 (3H, s, Me-2), 2.44 (2H, m, CH_2-4), 1.75 (4H, m, CH_2-5,6), 1.34 (3H, t, *J*=7.4 Hz, Me).

Ethyl 2-methyl-5-phenylpyrrole-3-carbodithioate (3d). 61%, orange crystals, mp 108°C; [Found: C, 64.11; H, 5.65; N, 5.08; S, 24.10. $C_{14}H_{15}NS_2$ requires C, 64.32; H, 5.78; N, 5.36; S, 24.53%]; ν_{max}(KBr) 3297, 2971, 2928, 2875, 1605, 1587, 1567, 1511, 1488, 1458, 1416, 1251, 1210, 1149, 1070, 1007, 985, 933, 901, 842, 790, 752, 707, 690, 637, 550, 493 cm^{-1}; δ_H (250.13 MHz, $CDCl_3$) 8.45 (1H, br s, NH), 7.45, 7.35, 7.23 (5H, m, Ph), 7.04 (1H, d, *J*=2.9 Hz, H-4), 3.33 (2H, q, *J*=7.4 Hz, SCH_2), 2.67 (3H, s, Me-2), 1.36 (3H, t, *J*=7.4 Hz, Me).

Ethyl 2-methyl-5-(2-furyl)pyrrole-3-carbodithioate (3e). 44%, orange crystals, mp 52°C; [Found: C, 56.75; H, 4.81; N, 4.89; S, 25.11. $C_{12}H_{13}NOS_2$ requires C, 57.34; H, 5.21; N, 5.57; S, 25.51%]; ν_{max}(KBr) 3407, 3270, 2965, 2924, 2861, 1625, 1545, 1510, 1454, 1419, 1369, 1331, 1231, 1203, 1007, 985, 960, 884, 837, 780, 725, 684, 588, 500 cm^{-1}; δ_H (250.13 MHz, $CDCl_3$) 8.68 (1H, br s, NH), 7.59 (1H, d, *J*=1.2 Hz, H-5 of furane), 6.96 (1H, d, *J*=2.7 Hz, H-4), 6.45 (2H, m, *J*=3.5, 1.6 Hz, H-3 and H-4 of furane), 3.32 (2H, q, *J*=7.4 Hz, SCH_2), 2.66 (3H, s, Me-2), 1.36 (3H, t, *J*=7.4 Hz, Me).

Ethyl 2-methyl-5-(2-thienyl)pyrrole-3-carbodithioate (3f). 46%, orange crystals, mp 64°C. [Found: C, 53.75; H, 4.81; N, 4.79; S, 35.41. $C_{12}H_{13}NS_3$ requires C, 53.89; H, 4.90; N, 5.24; S, 35.97%]; ν_{max}(KBr) 3367, 3112, 3064, 2965, 2923, 2868, 1598, 1521, 1458, 1419, 1365, 1338, 1237, 1194, 1146, 1014, 985, 834, 792, 682, 657, 587 cm^{-1}; δ_H (250.13 MHz, $CDCl_3$) 8.40 (1H, br s, NH), 7.17 (1H, dd, *J*=5.0, 1.2 Hz, H-5 of thiophene), 7.04 (1H, dd, *J*=3.5, 1.2 Hz, H-3 of thiophene), 7.00 (1H, dd, *J*=4.9, 3.5 Hz, H-4 of thiophene), 6.93 (1H, d, *J*=3.0 Hz, H-4), 3.32 (2H, q, *J*=7.4 Hz, SCH_2), 2.65 (3H, s, Me-2), 1.36 (3H, t, *J*=7.4 Hz, Me); δ_C (101.61 MHz, $CDCl_3$) 217.6, 135.0, 134.6, 130.5, 127.8, 124.4, 123.7, 121.8, 106.0, 29.5, 16.4, 13.00.

Ethyl 5-methylpyrrole-2-carbodithioate (3g). 46%, yellow crystals, mp 36°C; [Found: C, 50.96; H, 5.82; N, 7.89; S, 34.18. $C_8H_{11}NS_2$ requires C, 51.58; H, 5.98; N, 7.56; S, 34.61%]; ν_{max}(KBr) 3327, 2968, 2926, 2861, 1552, 1483, 1444, 1379, 1366, 1279, 1242, 1208, 1063, 1050, 1031, 1009, 976, 820, 779, 767, 684, 650, 615, 489, 431 cm^{-1}; δ_H (250.13 MHz, $CDCl_3$) 9.38 (1H, br s, NH), 6.99 (1H, dd, *J*=3.5 Hz, H-3), 6.02 (1H, dd, *J*=3.5 Hz, H-4), 3.35 (2H, q, *J*=7.4 Hz, SCH_2), 2.27 (3H, s, Me-5), 1.36 (3H, t, *J*=7.4 Hz, Me).

Ethyl 4,5-dimethylpyrrole-2-carbodithioate (3h). 51%, yellow crystals, mp 80°C; [Found: C, 54.03; H, 6.34; N, 6.67; S, 31.71. $C_9H_{13}NS_2$ requires C, 54.23; H, 6.57; N, 7.03; S, 32.17%]; ν_{max}(KBr) 3337, 2916, 2865, 2830, 1555, 1512, 1450, 1442, 1424, 1356, 1220, 1195, 1160, 1130, 1009, 976, 840, 830, 720, 680, 640, 500 cm^{-1}; δ_H (250.13 MHz, $CDCl_3$) 9.34 (1H, br s, NH), 6.86 (1H, d, *J*=2.56 Hz, H-3), 3.35 (2H, q, *J*=7.4 Hz, SCH_2), 2.17 (3H, s, Me-5), 1.98 (3H, s, Me-4), 1.34 (3H, t, *J*=7.4 Hz, Me).

Ethyl 3,5-dimethylpyrrole-2-carbodithioate (3i). 48%, yellow crystals, mp 96°C; [Found: C, 53.73; H, 6.18; N, 6.68; S, 31.63. $C_9H_{13}NS_2$ requires C, 54.23; H, 6.57; N, 7.03; S, 32.17%]; ν_{max}(KBr) 3307, 2966, 2927, 2865, 1553, 1469, 1418, 1371, 1240, 1190, 1144, 1022, 985, 974, 879, 821, 718, 682, 509, 469 cm^{-1}; δ_H (250.13 MHz, $CDCl_3$) 9.68 (1H, br s, NH), 5.92 (1H, d, *J*=2.40 Hz, H-3), 3.40 (2H, q, *J*=7.4 Hz, SCH_2), 2.45 (3H, s, Me-3), 2.23 (3H, s, Me-5), 1.39 (3H, t, *J*=7.4 Hz, Me).

Ethyl 5-(*tert*-butyl)-3-methylpyrrole-2-carbodithioate (3j). 62%, yellow crystals, mp 105°C; [Found: C, 59.34; H, 7.54; N, 5.43; S, 26.13. $C_{12}H_{19}NS_2$ requires C, 59.70; H, 7.93; N, 5.80; S, 26.56%]; ν_{max}(KBr) 3386, 2963, 2926, 2868, 1546, 1484, 1462, 1425, 1398, 1375, 1366, 1326, 1264, 1248, 1190, 1118, 1046, 1026, 1003, 989, 970, 881, 819, 802, 744, 709, 689, 678, 610, 537, 493, 478 cm^{-1}; δ_H (250.13 MHz, $CDCl_3$) 9.59 (1H, s, NH), 5.95 (1H, d, *J*=2.99 Hz, H-4), 3.38 (2H, q, *J*=7.4 Hz, SCH_2), 2.48 (3H, s, Me-3), 1.40 (3H, t, *J*=7.4 Hz, Me), 1.34 (9H, s, *t*-Bu).

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