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CHEMISTRY OF POLYHALOGENATED NITROBUTADIENES, 1: A NEW SYNTHESIS OF PERFUNCTIONALIZED 3-AMINO-4-NITROTHIOPHENES

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Abstract – An efficient synthesis of perfunctionalized 3-amino-4-nitrothiophenes was developed starting from highly chlorinated 2-nitrobutadiene derivatives. The key step of this new approach is the cyclization reaction of highly nucleophilic, ω-chlorinated butadienyl thiolates generated from 2-(2-diorganylamino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolanes upon action of base.

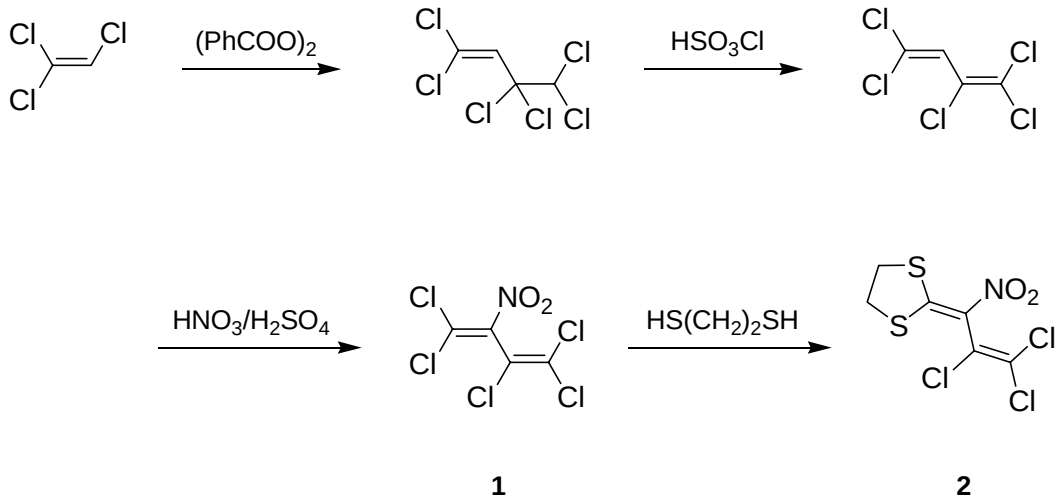
INTRODUCTION

In the course of our studies to introduce functionalized tri- or tetrachlorobutadienes as versatile building blocks for the synthesis of heterocyclic compounds, we have accomplished a new domino reaction of 2-(2-diorganylamino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolanes to give persubstituted 3-amino-4--nitrothiophenes. Our interest in such thiophene derivatives primarily derives from their manifold bioactivities; e.g., some 4-nitrothiophenes show antibacterial,[1,2] antiarrhythmic,[3] antihypoxic,[4] protozoicide and anthelmintic activity,[5] or have been proven to be potent bacteriostatics or mycostatics.[6] In addition, 2-chlorothiophenes have been shown to be anticonvulsant,[7] antiviral,[8] or fungicidal compounds.[9] In additional investigations, they were effective as inhibitor of herpes simplex protease HSV-2,[10] as well as against ascitic murine colon adeno carcinoma MAC 15A cell lines.[11] Finally, the anti-HIV-1[12] and antitumor activity[13] of some 2-chlorothiophenes should be emphasized. Additionally, material science based fields of application are conceivable: these thiophene derivatives can serve as structural unit in both, dyes similar to the thioindigo system[14] as well as in polythiophenes, acting as organic conductors with an internal, repititive electronic *push-pull* system.[15]

RESULTS AND DISCUSSION

The synthesis of thiophene derivatives either involves subsequent functionalization of the parent ring system or, alternatively, cyclization of an appropriate acyclic precursor. In our synthetic approach, 1,1,2,4,4-pentachloro-3-nitrobuta-1,3-diene (**1**), the most important representative of nitro-substituted polyhalogenated 1,3-butadienes,[16-18] serves as the starting material. It is easily accessible from trichloroethylene by radical dimerization, subsequent dehydrochlorination and, finally, nitration as published by Kaberdin *et al.*[19] (see Scheme 1).

Scheme 1

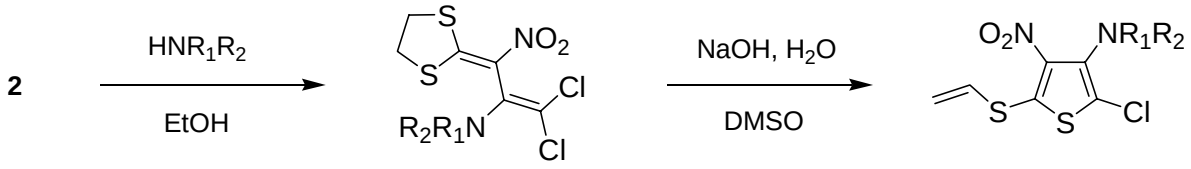


1 **2**

In compound (**1**) the significantly electrophilic character of the C-4 position due to the α-nitro group permits a smooth, regioselective substitution of these terminal vinylic chloro substituents with good nucleophiles such as mercaptans. Therefore, introduction of dithiols such as 1,2-ethanedithiol or 1,3-propanedithiol leads to the cyclic 1,1-bissubstituted heterocycles, 2-(2,3,3-trichloro-1-nitroallylidene)-[1,3]dithiolane (**2**),[20] or the corresponding dithiane, respectively. Under basic conditions these dithiolanes are known to be less stable than the similar dithiane derivatives[21] which were used by Seebach and others for Umpolung reactions[22] of the corresponding carbonyl compounds. We have now used the lability of such [1,3]dithiolanes in the presence of a strong base as a key step of our new thiophene synthesis: The first step of this sequence is the regioselective nucleophilic substitution of the vinylic chloro substituents adjacent to the nitro group. Applying an excess of cyclic or acyclic secondary amines, the corresponding 2-(2-diorganylamino-3,3-dichloro-1-nitroallylidene)- [1,3]dithiolanes (**3**) can be prepared in yields ranging from 30 to 90% (see Scheme 2). Structural assignments of these stable, red or orange solids or oils were achieved, mainly, by means of ^{13}C-NMR spectroscopy. These data are given in Table 1. The key step of subsequent cyclization is initiated upon addition of a base (30% aqueous sodium hydroxide) to **3a-n**. Usually, this reaction is performed in dimethyl sulfoxide at 0°C within 2 to 6 h. After

protic work up, the 3-amino-2-chloro-4-nitro-5-vinylsulfanylthiophenes (**4a-n**) were isolated as red or orange crystalline solids. Mechanistical suggestions are depicted in Scheme 3: In accordance with a similar vinyl sulfide formation from EWG-substituted dithiolanes published by Schaumann *et al.*,[23] the initial deprotonation in α-position to the sulfur atom leads to ring scission and generates the highly nucleophilic α-vinylsulfanyl-substituted dienyl thiolate which, eventually, attacks the *gem*-dichlorovinyl group under substitution.

Scheme 2



3a-n

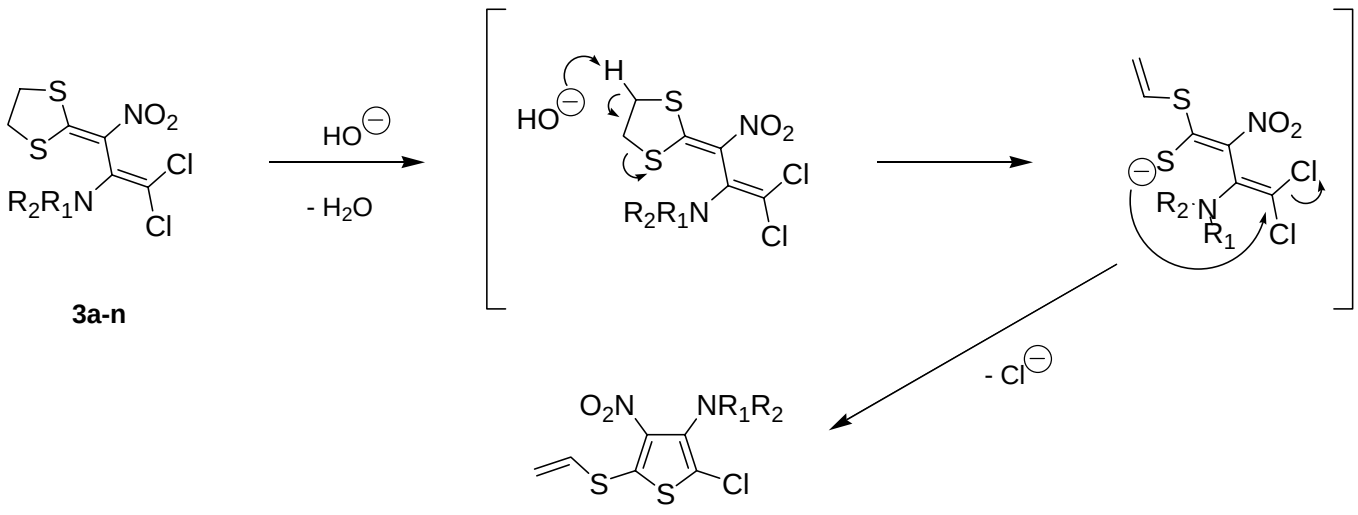
30-90% yield

4a-n

60-90% yield

3a, **4a**:	R_1=R_2=Me	**3h**, **4h**:	R_1R_2=$(CH_2)_6$
3b, **4b**:	R_1=R_2=Et	**3i**, **4i**:	R_1R_2=$(CH_2)_7$
3c, **4c**:	R_1=R_2=*n*-Bu	**3j**, **4j**:	R_1R_2=$(CH_2)_2O(CH_2)_2$
3d, **4d**:	R_1=R_2=cyclohexyl	**3k**, **4k**:	R_1R_2=$CHMe(CH_2)_3CHMe$
4e:	R_1=Me, R_2=Bn	**3l**, **4l**:	R_1R_2=1,4-dioxa-8-azaspiro[4,5]decyl-8-yl
3f, **4f**:	R_1R_2=$(CH_2)_4$	**3m**, **4m**:	R_1R_2=4-benzylpiperazo
3g, **4g**:	R_1R_2=$(CH_2)_5$	**3n**, **4n**:	R_1R_2=4-(3-chlorophenyl)piperazo

Scheme 3

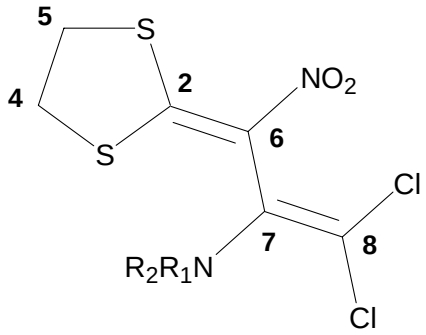


3a-n

4a-n

60-90% yield

Table 1: ^{13}C-NMR spectral data of 2-amino-3-nitrobutadienes (**3a-n**)



^{13}C-NMR spectral data, δ-values						
Compd	C-2	C-4, C-5	C-6	C-7	C-8	other carbon atoms
3a[a)]	170.8	39.8, 37.5	130.7	139.9	108.1	41.4 (NCH_3)
3b[a)]	169.5	39.6, 37.7	132.1	138.9	109.8	45.1 (NCH_2) , 13.7 (CH_3)
3c[b)]	173.0	40.0, 38.3	130.6	139.8	107.0	51.3 (NCH_2), 30.4 (CH_2), 19.8 (CH_2), 14.0 (CH_3)
3d[b)]	171.1	40.0, 38.3	132.8	139.6	115.5	60.7 (NCH), 33.2 (CH_2), 26.5 (CH_2), 25.6 (CH_2)
3f[b)]	172.7	40.4, 38.1	129.8	138.1	100.4	50.3 (NCH_2), 25.0 (CCH_2)
3g[b)]	173.7	40.3, 38.1	129.8	140.5	108.9	50.3 (NCH_2), 25.8 (2C,CCH_2), 23.9 (1C,CCH_2)
3h[a)]	170.1	39.7, 37.5	131.4	140.2	107.3	52.2 (NCH_2), 28.8 (2C,CCH_2), 27.3 (2C,CCH_2)
3i[b)]	173.2	40.2, 38.3	130.1	140.8	106.8	53.1 (NCH_2), 28.3 (2C,CCH_2), 27.0 (1C,CH_2), 24.1 (2C,CCH_2)
3j[b)]	174.5	40.5, 38.2	129.1	139.8	110.5	66.3 (OCH_2), 49.4 (NCH_2)
3k[b)]	173.0	40.2, 38.2	131.1	140.0	106.3	51.4 (NCH), 30.1 (CH<u>C</u>H_2), 21.9 (NCH_3), 14.4 (1C,CH_2)
3l[b)]	174.0	40.4, 38.2	129.6	139.9	109.9	106.2 (OCO), 63.9 (OCH_2), 47.5 (NCH_2), 34.9 (CCH_2)
3m[b)]	174.0	40.4, 38.2	129.5	138.0	109.7	139.9 ($C_{quat.}$, Ph), 129.0 (2C, Ph), 128.3 (2C, Ph), 127.1 (1C, Ph), 62.1 (Ph<u>C</u>H_2), 52.7, 49.0 (N**C**H_2)
3n[a)]	171.2	40.0, 37.6	130.3	138.8	113.0	151.9 ($NC_{quat.}$), 134.6 (CCl), 130.0 (*m*-CH), 119.4 (*p*-CH), 115.7 (CCl-<u>C</u>H-CN), 114.1 (*o*-CH), 48.8 (NCH_2), 48.7 (NCH_2)

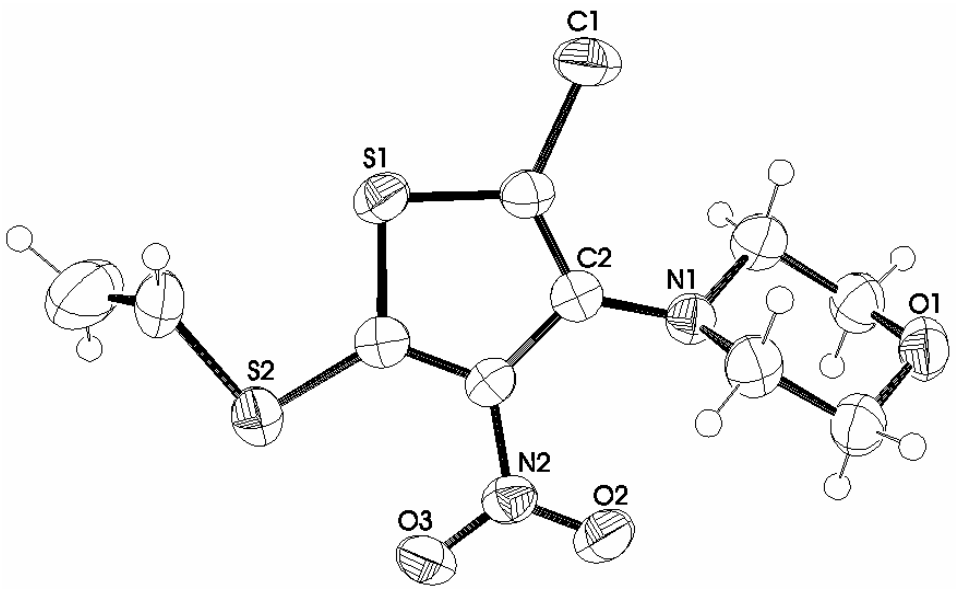
[a)]$CDCl_3$ (77.0 ppm), [b)]DMSO-d_6 (39.7 ppm)

Accompanied by withdrawal of a chloride anion, the sequence ends up in an intramolecular ring formation of this highly functionalized thiophene. The chemical yields range from acceptable to very good (60 to 90%), whereas a similar approach applying phosphovinyl thiolates has been published by Minami and co-workers to give 4,5-dihydrothiophenes in 12% and 24% yields, only.[24]

From a synthetic point of view it is important to note that this sequence was also performed as a one-pot reaction. For example, with benzylmethylamine as the organic base, we started at 75°C in DMSO to generate **3e**. After 5 h the mixture was cooled down to 0°C and treated with aqueous sodium hydroxide to initiate the cyclization step. In this case, the overall yield of **4e** was 40% .

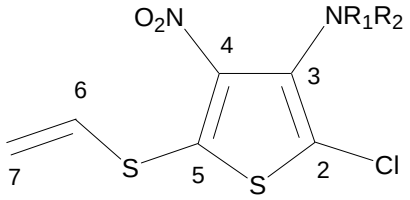
In case of 2-chloro-3-morpholino-4-nitro-5-vinylsulfanylthiophene (**4j**), we were fortunate to carry out an X-Ray crystallographic analysis[25, 26] to prove the structural conclusions that we had drawn from the nmr spectra (see Figure 1).

Figure 1: X-Ray structure of 2-chloro-3-morpholino-4-nitro-5-vinylsulfanylthiophene (**4j**)



To investigate the scope of this reaction we varied from mono- to bisamines. For example, reacting **2** with piperazine the expected bis-compound (**5**) was obtained in 50% yield. Subsequent twofold thiolate-cyclization furnished the bis(3-thienyl)piperazine derivative (**6**) (82% yield). Furthermore, compound (**6**) was selectively oxidized to the bis(vinylsulfoxide) (**7**) upon treatment with *m*-chloroperbenzoic acid in dichloromethane (70% yield).

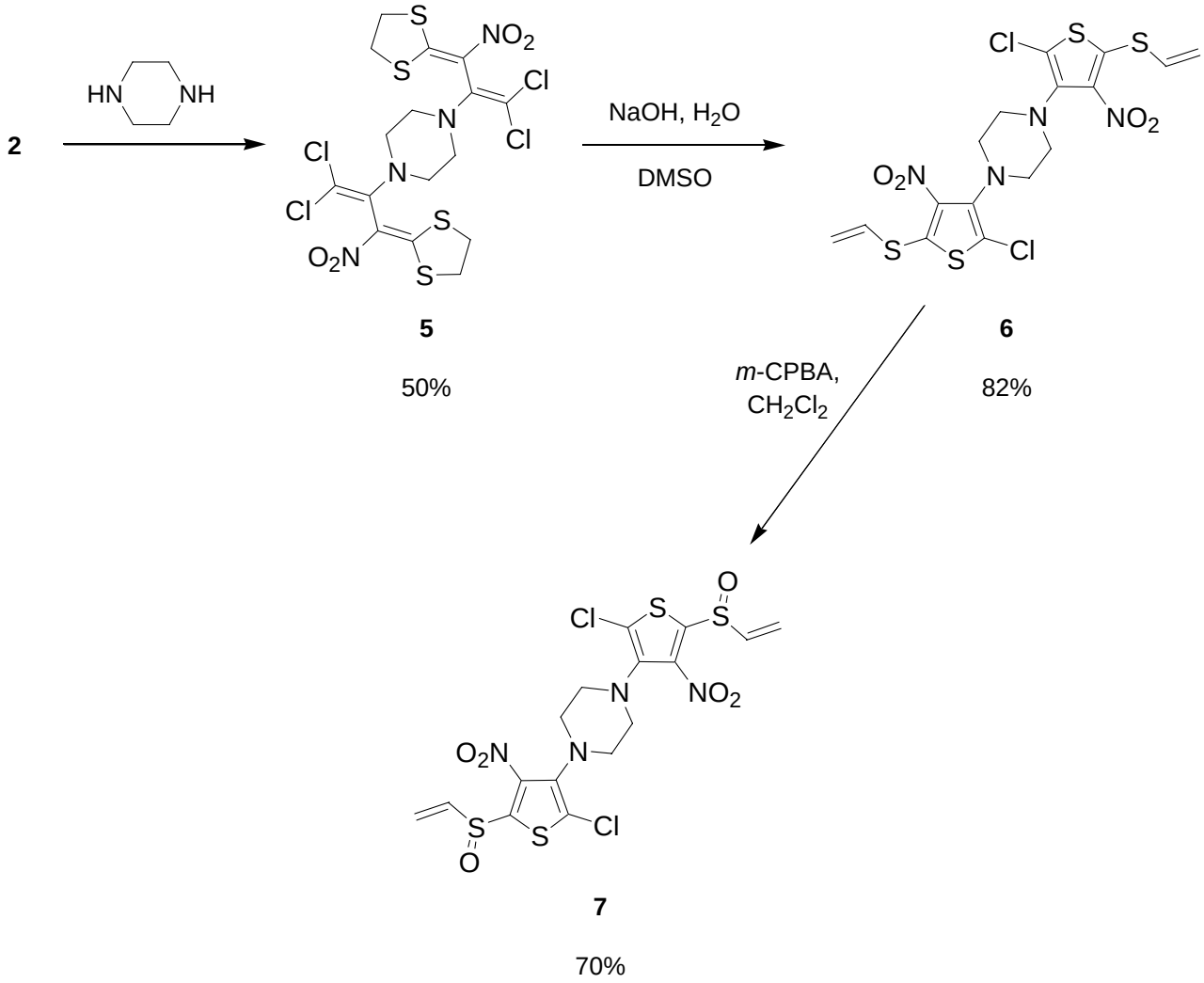
Table 2: ^{13}C-NMR spectral data of thiophenes (**4a-n**)



	^{13}C-NMR spectral data, δ-values						
Compd	C-2	C-3	C-4	C-5	C-6	C-7	other carbon atoms
4a[a)]	118.7	142.4	139.5	140.5	126.7	125.9	42.3 (NCH_3)
4b[a)]	123.2	139.8	140.8	140.4	126.9	125.8	47.2 (NCH_2), 14.0 (CH_3)
4c[a)]	122.0	140.9	140.2	141.0	126.9	126.0	53.2 (NCH_2), 31.0 (CH_2), 20.1 (CH_2), 13.9 (CH_3)
4d[a)]	128.3	137.7	143.4	137.6	127.3	125.3	58.8 (NCH), 33.6, 32.3, 25.9, 25.8 (CH_2)
4e[a)]	121.2	141.2	139.7	142.1	126.7	126.2	138.2 ($C_{quat.}$), 128.3,128.2 (4CH, Ph), 127.2 (1CH, Ph), 58.8 (NCH_2), 39.6 (NCH_3)
4f[a)]	117.7	139.3	139.9	139.7	127.1	125.4	50.6 (NCH_2), 26.0 ($C\underline{C}H_2$)
4g[a)]	117.9	142.3	139.9	139.3	127.1	125.3	51.3 (NCH_2), 28.4 (2C,$C\underline{C}H_2$), 23.9 (1C,$C\underline{C}H_2$)
4h[a)]	121.4	140.9	139.6	143.6	126.8	126.1	53.0 (NCH_2), 30.5 ($C\underline{C}H_2$), 27.7 ($C\underline{C}H_2$)
4i[a)]	122.9	141.5	139.8	143.9	126.8	126.2	54.0 (NCH_2), 28.8 (2C, $C\underline{C}H_2$), 26.7 (1C, $C\underline{C}H_2$), 25.9 (2, $C\underline{C}H_2$)
4j[a)]	119.3	140.7	139.3	141.0	126.7	126.2	67.4 (OCH_2), 50.2 (NCH_2)
4k[a)]	121.4	142.3	140.6	138.4	126.8	126.9	54.5 (NCH), 35.3 (2C, $C\underline{C}H_2$), 24.5 (1C, $C\underline{C}H_2$), 20.5 (NCH_3)
4l[a)]	118.0	140.5	139.3	141.6	126.9	125.9	106.9 ($C_{quat.}$), 64.3 (OCH_2), 48.6 (NCH_2), 35.8 (CCH_2)
4m[b)]	118.5	138.1	129.8	142.9	129.7	128.1	139.8 ($C_{quat.}$), 131.8, 129.0 (4CH, Ph), 126.5 (1CH, Ph), 58.9 (NCH_2Ph), 51.5 (NCH_2), 46.8 (NCH_2)
4n[a)]	119.1	140.8	139.2	141.2	126.7	126.4	152.2 ($NC_{quat.}$), 134.9 ($C_{quat.}Cl$), 130.0, 119.8, 116.3, 114.5 (4CH, Ph), 49.9, 49.8 (NCH_2)

[a)]$CDCl_3$ (77.0 ppm), [b)]DMSO-d_6 (39.7 ppm)

Scheme 4



Due to their high functionality, these 5-thio-substituted 3-amino-2-chloro-4-nitrothiophenes are key intermediates with high synthetical potential. Three different types of conversions seem to be most promising, starting from the given substitution pattern:

- *Chloro substituent* (C-2)

Besides selective reduction, e.g. by lithiation and subsequent protonation,[27] C,C-coupling reactions at this position, e.g. by palladium-[28, 29] or cobalt-catalysis[35,36] (homo-coupling) as well as lithium-[30,31] or nickel-mediation[32,33] are challenging. In addition, substitution reactions e.g. with amines at the C-2 position should be interesting, either in an intermolecular,[37] or an intramolecular pathway.[38]

- *Conversion of the vinylsulfanyl moiety*

After selective, twofold oxidation of the sulfanyl-sulfur atom, e.g. with *m*-chloroperbenzoic acid or hydrogen peroxide,[39] or with potassium hydrogenperoxomonosulfate,[40] this vinyl sulfone may either serve as a valuable cyclophile for cycloaddition reactions or as a good leaving group in reductive cleavage reactions.

- *Modification of the push-pull subunit*

Apart from its own value,[15] the reduction of the nitro group would open synthetic access to interesting thiophene-annelated diazaheterocyclic compounds, such as rare thienopyrazine or thienoimidazole derivatives.

In conclusion, we have developed a short and efficient synthesis of 3-amino-2-chloro-4-nitro-5-vinylsulfanylthiophenes that can also be performed as a one-pot reaction. Various consecutive synthetic steps are conceivable leading either to useful chemical precursors and/or physiologically active key compounds or even interesting building blocks for organic conductors or materials. Biological testings of these unknown substances are underway, thiophene derivative (**4g**) showed nematicidal activity, already.

EXPERIMENTAL

Melting points were measured on a Büchi 520 apparatus and were uncorrected. ^{1}H-, ^{13}C-, ^{14}N-, and ^{15}N-NMR spectra were obtained on a BRUKER Avance with 400 MHz proton frequency. ^{1}H-NMR spectra in $CDCl_3$ were referenced to tetramethylsilane (TMS) at 0.0 ppm; ^{13}C-NMR spectra refer to the solvent signal center at 77.0 ppm. In case of DMSO-d_6, the solvent peak was set to 2.50 ppm (^{1}H) and 39.70 ppm (^{13}C), respectively. N-NMR spectra were externally referenced to nitromethane at 0.0 ppm. Coupling constants are given in Hertz. IR spectra were obtained on a BRUKER "Vector 22" FT IR as film between NaCl plates or as KBr IR. Mass spectra were recorded on a Hewlett Packard – System 'MS 5989B' with direct inlet. All masses of chlorine containing molecules or fragments refer to the isotope ^{35}Cl. High-resolution mass spectra were measured with a Varian MAT 311 A spectrometer with pre-selected molecular ion peak matching at R >> 10000 to be within ± 2 ppm of the exact masses. TLC was carried out on Merck-plates coated with silica gel (60 F 254). Silica gel 60 was also used for column chromatography. 2-Nitropentachloro-1,3-butadiene (**1**) was prepared in 53% yield (bp 69-71°C) following the literature.[41]

2-(2,3,3-Trichloro-1-nitroallylidene)-[1,3]dithiolane (**2**). A solution of 22.0 mL (262 mmol) of 1,2-ethanedithiol in 41.4 mL (260 mmol) of **1** was stirred for 2 days at rt. After addition of 100 mL of petrol ether and stirring for additional 20 min, the precipitate was collected and washed successive with water, aqueous sodium hydrogencarbonate, again water, and then petrol ether. After drying *in vacuo* **2** was obtained in 92% yield (70 g); mp 116-117°C (petrol ether : dichloromethane = 1 : 1), (lit[20]: mp 110-112°C).

*General procedure for the preparation of the 2-(2-organylamino-3,3-dichloro-1-nitro-allylidene)-[1,3]dithiolanes (**3a-n**). Procedure A.*
To a stirred suspension of 1.00 g (3.42 mmol) of **2** in 20 mL of EtOH was added 18.00 mmol of the secondary amine at 10°C within 10 min. Depending on the substrate, the mixture was stirred at 20-78°C for 5 to 120 h. After cooling to rt, either the product was isolated as a solid, or a viscous oil was obtained after extraction with trichloromethane, subsequent drying over anhydrous sodium sulfate and evaporation of the solvent.

*2-(2-Dimethylamino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolane (**3a**)*. Reaction time: 10 h at 40-45°C. Yield: 80%, mp 103-105°C (MeOH). IR (KBr): 2931, 1584, 1523 (NO_2), 1459, 1270 (NO_2), 1076, 977, 912, 837, 777, 719 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 3.61 m (total 4H, C_4-H, C_5-H), 2.73 s (total 6H, NCH_3, $^1J_{C,H}$ = 136 Hz).

*2-(2-Diethylamino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolane (**3b**)*. Reaction time: 8 h at 60-65°C. Yield: 75%, orange oil. R_f =0.35 (ethyl acetate : ether = 1 : 3). IR (film): 2976, 1574, 1520 (NO_2), 1463, 1276 (NO_2), 1086, 1009, 926, 851, 780, 718 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 3.55 m (total 4H, C_4-H, C_5-H), 3.05 q (total 4H, NCH_2, J = 7.1 Hz), 1.11 t (total 6H, CH_3, J = 7.1 Hz). HREIMS calcd for $C_{10}H_{14}N_2O_2Cl_2S_2$ 327.9874, found: *m/z* 327.9874.

*2-(2-Di(n-butyl)amino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolane (**3c**)*. Reaction time: 10 h at 60-65°C. Yield: 70%, mp 53-55°C (MeOH). IR (KBr): 2961, 1578, 1514 (NO_2), 1455, 1276 (NO_2), 1096, 971, 919, 767, 723 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.66 br s (total 4H, C_4-H, C_5-H), 2.91 m (total 4H, NCH_2), 1.46 m (total 4H, CH_2), 1.23 m (total 4H, CH_2), 0.86 t (total 6H, CH_3, J = 7.2 Hz). MS: *m/z* 384 [M^+]. *Anal.* Calcd for $C_{14}H_{22}N_2O_2Cl_2S_2$: C, 43.63; H, 5.75; N, 7.27; Cl, 18.40; S, 16.64. Found: C, 43.64; H, 5.74; N, 7.20; Cl, 18.13; S, 16.65.

*2-(2-Di(cyclohexyl)amino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolane (**3d**)*. Reaction time: 90 h at 78°C. Yield: 30%, mp 183-185°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2930, 1531 (NO_2), 1466,

1296 (NO_2), 1110, 975, 907, 874, 779, 754, 710, 664 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.63 br s (total 4H, C_4-H, C_5-H), 2.90 m (total 2H, NCH), 1.71 m (total 8H, CH_2), 1.53 m (2H, CH_2), 1.24 m (total 8H, CH_2), 0.98 m (2H, CH_2). HREIMS calcd for $C_{18}H_{26}N_2O_2Cl_2S_2$ 436.0813, found: *m/z* 436.0813.

*2-(2-Pyrrolidino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolane (**3f**)*. Reaction time: 6 h at 20°C. Yield: 90%, mp 115-116°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2966, 2870, 1590, 1521 (NO_2), 1459, 1366,1281 (NO_2), 986, 913, 814, 769, 721 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.69 br s (total 4H, C_4-H, C_5-H), 3.12 m (total 4H, NCH_2), 1.77 m (total 4H, CCH_2). HRESIMS calcd for $C_{10}H_{13}N_2O_2Cl_2S_2$ $(M+H)^+$ 326.9790, found: *m/z* 326.9789.

*2-(2-Piperidino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolane (**3g**)*. Reaction time: 10 h at 50-55°C. Yield: 90%, mp 105-107°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2941, 2846, 1582, 1514 (NO_2), 1454, 1278 (NO_2), 1105, 964, 953, 794, 762, 719 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.68 br s (total 4H, C_4-H, C_5-H), 2.90 m (total 4H, NCH_2), 1.47 m (total 6H, CCH_2). MS: *m/z* 340 [M^+]. ***Anal.*** Calcd for $C_{11}H_{14}N_2O_2Cl_2S_2$: C, 38.71; H, 4.13; N, 8.21; Cl, 20.78; S, 18.79. Found: C, 38.88; H, 4.20; N, 8.31; Cl, 20.15; S, 18.97.

*2-(2-Hexamethylenimino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolane (**3h**)*. Reaction time: 30 h at 50-55°C. Yield: 50%, orange oil. R_f =0.50 (ethyl acetate : petrol ether = 1:1). IR (film): 2928, 2854, 1578, 1525 (NO_2), 1456, 1273 (NO_2), 1007, 937, 774, 710 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 3.60 br s (total 4H, C_4-H, C_5-H), 3.14 m (total 4H, NCH_2), 1.60 m (total 8H, CCH_2).

*2-(2-Heptamethylenimino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolane (**3i**)*. Reaction time: 45 h at 50-55°C. Yield: 83%, mp 60-62°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2919, 2847, 1580, 1519 (NO_2), 1452, 1271 (NO_2), 1149, 1095, 977, 913, 875, 763, 708 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.69 br s (total 4H, C_4-H, C_5-H), 3.08 m (total 4H, NCH_2), 1.58 m (total 10H, CCH_2). HREIMS calcd for $C_{13}H_{18}N_2O_2Cl_2S_2$ 368.0187, found: *m/z* 368.0187.

*2-(2-Morpholino-3,3-dichloro-1-nitroallylidene)-[1,3]dithiolane (**3j**)*. Reaction time: 70 h at 60-65°C. Yield: 80%, mp 139-141°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2973, 2857, 1585, 1512 (NO_2), 1447, 1272 (NO_2), 1024, 970, 925, 862, 802, 766, 719 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.70 br s (total 4H, OCH_2), 3.60 t (total 4H, C_4-H, C_5-H, J = 4.6 Hz), 2.94 m (total 4H, NCH_2). HREIMS calcd for $C_{10}H_{12}N_2O_3Cl_2S_2$ 341.9666, found: *m/z* 341.9666.

*1-[2,2-Dichloro-1-([1,3]dithiolan-2-ylidene-nitromethyl)vinyl]-2,6-dimethylpiperidine (**3k**)*. Reaction time: 120 h at 78°C with additional 3.50 mmol EtONa. Yield: 48%, mp 103-104°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2926, 1556, 1514 (NO_2), 1452, 1268 (NO_2), 1105, 1053, 979, 905, 779, 756, 700 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.67 br s (total 4H, C_4-H, C_5-H), 3.44 m (total 2H, NCH), 1.77-1.38 m (total 6H, CCH_2),1.22 d (total 6H, CH_3, J = 7.1 Hz). HREIMS calcd for $C_{13}H_{18}N_2O_2Cl_2S_2$ 368.0187, found: *m/z* 368.0187.

8-[2,2-Dichloro-1-([1,3]dithiolan-2-ylidene-nitromethyl)vinyl]-1,4-dioxa-8-azaspiro[4.5]decane (***3l***). Reaction time: 30 h at 50-55°C. Yield: 85%, mp 112-114°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2960, 2848, 1582, 1506 (NO_2), 1460, 1394, 1271 (NO_2), 1083, 1031, 974, 851, 809, 766, 718 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.86 br s (total 4H, OCH_2), 3.69 br s (total 4H, C_4-H, C_5-H), 3.01 m (total 4H, NCH_2), 1.63 m (total 4H, CCH_2). MS: *m/z* 398 [M^+]. *Anal.* Calcd for $C_{13}H_{16}N_2O_4Cl_2S_2$: C, 39.10; H, 4.04; N, 7.02; Cl, 17.76; S, 16.06. Found: C, 39.35; H, 4.09; N, 7.05; Cl, 17.64; S, 16.10.

*2-[2-(4-Benzylpiperaz-1-yl)-3,3-dichloro-1-nitroallylidene]-[1,3]dithiolane (**3m**)*. Reaction time: 100 h at 60-65°C. Yield: 85%, mp 45-47°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2933, 2809, 1583, 1523 (NO_2), 1454, 1272 (NO_2), 1139, 1034, 1006, 969, 821, 777, 741, 699 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 7.28 br s (5H, Ph), 3.68 br s (total 4H, C_4-H, C_5-H), 3.46 br s (2H, Ph$C\underline{H}_2$), 2.97 m (total 4H, NCH_2), 2.37 m (total 4H, NCH_2). HREIMS calcd for $C_{17}H_{19}N_3O_2Cl_2S_2$ 431.0296, found: *m/z* 431.0296.

*2-[2-(3-Chlorophenylpiperaz-4-yl)-3,3-dichloro-1-nitroallylidene]-[1,3]dithiolane (**3n**)*. Reaction time: 100 h at 60-65°C. Yield: 60%, mp 117-119°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2837, 1594, 1521 (NO_2), 1383, 1275 (NO_2), 1138, 1027, 987, 910, 814, 777, 732 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 7.15 m (1H, *m*-Ph), 6.80 m (3H, Ph), 3.57 m (total 4H, C_4-H, C_5-H), 3.18 br s (total 8H, NCH_2). HREIMS calcd for $C_{16}H_{16}N_3O_2Cl_3S_2$ 450.9749, found: *m/z* 450.9749.

General procedure for the synthesis of 2-chloro-3-organylamino-4-nitro-5-vinylsulfanylthiophenes (**4a-n**).
Procedure B.

Over a period of 10 min at 0°C 1.00 g of an aqueous solution of sodium hydroxide in water (40%, 10.0 mmol) was added to 2.00 mmol dithiolane (**3a-n**) dissolved in 10 mL DMSO. After 1 h at 0°C the mixture was stirred for additional 2 to 10 h at rt. Then cold water (70 mL) was added at 0 to 5°C. The mixture was acidified to pH 1 upon dropwise addition of concentrated hydrochloric acid. In case no precipitation occurs, the extraction-method as described in Procedure A is applied.

2-Chloro-3-dimethylamino-4-nitro-5-vinylsulfanylthiophene ***(4a).*** Reaction time: 5 h. Yield: 80%, mp 33-34°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2933, 2799, 1547 (NO_2), 1329 (NO_2), 1212, 1120, 998, 959, 845, 722 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.46 dd (1H, C_6-H, J = 16.4, 9.2 Hz, $^1J_{C,H}$ = 176 Hz), 5.78 d (1H, C_7-H_{trans}, J = 16.4 Hz, $^1J_{C,H}$ = 161 Hz), 5.74 d (1H, C_7-H_{cis}, J = 9.2 Hz, $^1J_{C,H}$ = 162 Hz), 2.76 s (total 6H, Me, $^1J_{C,H}$ = 134 Hz). HREIMS calcd for $C_8H_9N_2O_2ClS_2$ 263.9794, found: *m/z* 263.9794.

2-Chloro-3-diethylamino-4-nitro-5-vinylsulfanylthiophene ***(4b)***. Yield: 70%, mp 45-46°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2969, 2865, 1539 (NO_2), 1320 (NO_2), 1210, 963, 931, 787, 720 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.56 dd (1H, C_6-H, J = 16.4, 9.2 Hz), 5.87 d (1H, C_7-H_{trans}, J = 16.4 Hz), 5.83 d (1H, C_7-H_{cis}, J = 9.2 Hz), 3.13 q (total 4H, NCH_2, J = 7.2 Hz, $^1J_{C,H}$ = 136 Hz), 1.02 t (total 6H, Me, J = 7.2 Hz, $^1J_{C,H}$ = 126 Hz). HREIMS calcd for $C_{10}H_{13}N_2O_2ClS_2$ 292.0107, found: *m/z* 292.0107.

2-Chloro-3-di(n-butyl)amino-4-nitro-5-vinylsulfanylthiophene ***(4c)***. Yield: 65%, mp 45-46°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2956, 2863, 1542 (NO_2), 1328 (NO_2), 1036, 958, 720 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.57 dd (1H, C_6-H, J = 16.3, 9.3 Hz), 5.88 d (1H, C_7-H_{trans}, J = 16.3 Hz), 5.83 d (1H, C_7-H_{cis}, J = 9.3 Hz), 3.05 m (total 4H, NCH_2), 1.31 m (total 8H, CH_2), 0.87 t (total 6H, Me, J = 7.2 Hz). HREIMS calcd for $C_{14}H_{21}N_2O_2ClS_2$ 348.0733, found: *m/z* 348.0733.

2-Chloro-3-di(cyclohexyl)amino-4-nitro-5-vinylsulfanylthiophene ***(4d)***. Yield: 80%, mp 58-59°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2926, 2852, 1538 (NO_2), 1488, 1321 (NO_2), 1128, 1059, 990, 911, 716, 706 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.48 dd (1H, C_6-H, 16.4, 9.2 Hz), 5.76 d (1H, C_7-H_{trans}, J = 16.4 Hz), 5.72 d (1H, C_7-H_{cis}, J = 9.1 Hz), 3.12 m (total 2H, NCH), 1.94 m (2H, CH_2), 1.62 m (total 8H, CH_2), 1.00 m (total 10H, CH_2). HREIMS calcd for $C_{18}H_{25}N_2O_2ClS_2$ 400.1046, found: *m/z* 400.1046.

2-Chloro-3-methylbenzylamino-4-nitro-5-vinylsulfanylthiophene ***(4e)***. Yield: 40% (two steps). Viscous oil. R_f = 0.50 (ether : petrol ether = 1:3). IR (film): 3028, 2806, 1542 (NO_2), 1328 (NO_2), 1162, 1097, 961, 855, 786, 699 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 7.34 m (5H, Ph), 6.53 dd (1H, C_6-H, J = 16.3, 9.1 Hz), 5.85 d (1H, C_7-H_{trans}, J = 16.3 Hz), 5.81 d (1H, C_7-H_{cis}, J = 9.1 Hz), 4.20 br s (2H, NCH_2, $^1J_{C,H}$ = 136 Hz), 2.74 br s (3H, NCH_3, $^1J_{C,H}$ = 136 Hz). HREIMS calcd for $C_{14}H_{13}N_2O_2ClS_2$ 340.0107, found: *m/z* 340.0107.

2-Chloro-3-pyrrolidino-4-nitro-5-vinylsulfanylthiophene ***(4f)***. Yield: 75%, mp 63-64°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2971, 2866, 1543 (NO_2), 1490, 1351, 1315 (NO_2), 1049, 1019, 972, 867, 720 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.54 dd (1H, C_6-H, J = 16.4, 9.2 Hz), 5.84 d (1H, C_7-H_{trans}, J =

16.4 Hz), 5.79 d (1H, C_7-H_{cis}, J = 9.2 Hz), 3.28 m (total 4H, NCH_2), 1.95 m (total 4H, CCH_2). HRESIMS calcd for $C_{10}H_{12}N_2O_2ClS_2$ $(M+H)^+$ 291.0023, found: *m/z* 291.0025.

*2-Chloro-3-piperidino-4-nitro-5-vinylsulfanylthiophene (**4g**)*. Yield: 90%, mp 59-60°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2936, 2848, 1539 (NO_2), 1483, 1377, 1315 (NO_2), 1048, 982, 960, 853, 804, 724 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.53 dd (1H, C_6-H, J = 16.3, 9.0 Hz), 5.83 d (1H, C_7-H_{trans}, J = 16.3 Hz), 5.78 d (1H, C_7-H_{cis}, J = 9.0 Hz), 3.11 m (total 4H, NCH_2), 1.62 m (total 6H, CCH_2). HREIMS calcd for $C_{11}H_{13}N_2O_2ClS_2$ 304.0107, found: *m/z* 304.0107.

*2-Chloro-3-hexamethylenimino-4-nitro-5-vinylsulfanylthiophene (**4h**)*. Yield: 70%, mp 56-57°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2923, 2847, 1546 (NO_2), 1483, 1388, 1326 (NO_2), 1041, 998, 962, 808, 716 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.56 dd (1H, C_6-H, J = 16.4, 9.1 Hz), 5.88 d (1H, C_7-H_{trans}, J = 16.4 Hz), 5.82 d (1H, C_7-H_{trans}, J = 9.1 Hz), 3.11 m (total 4H, NCH_2), 1.70 m (total 8H, CCH_2). MS: *m/z* 318 [M^+]. *Anal.* Calcd for $C_{12}H_{15}N_2O_2ClS_2$: C, 45.20; H, 4.74; N, 8.79; Cl, 11.12; S, 20.11. Found: C, 45.43; H, 4.92; N, 9.00; Cl, 11.17; S, 19.58.

*2-Chloro-3-heptamethylenimino-4-nitro-5-vinylsulfanylthiophene (**4i**)*. Yield: 90%, mp 73-75°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2919, 2850, 1544 (NO_2), 1489, 1447, 1325 (NO_2), 1135, 1030, 995, 952, 906, 789, 717 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.56 dd (1H, C_6-H, J = 16.3, 9.2 Hz, $^1J_{C,H}$ = 177 Hz), 5.89 d (1H, C_7-H_{trans}, J = 16.3 Hz), 5.83 d (1H, C_7-H_{cis}, J = 9.2 Hz), 3.08 m (total 4H, NCH_2), 1.65 m (total 10H, CCH_2). HREIMS calcd for $C_{13}H_{17}N_2O_2ClS_2$ 332.0420, found: *m/z* 332.0420.

*2-Chloro-3-morpholino-4-nitro-5-vinylsulfanylthiophene (**4j**)*. Yield: 85%, mp 76-78°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2967, 2852, 1543 (NO_2), 1491, 1367, 1321 (NO_2), 1259, 1117, 1022, 993, 961, 857, 725 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.47 dd (1H, C_6-H, J = 16.4, 9.2 Hz), 5.81 d (1H, C_7-H_{trans}, J = 16.4 Hz), 5.76 d (1H, C_7-H_{cis}, J = 9.2 Hz), 3.71 m (total 4H, OCH_2), 3.13 m (total 4H, NCH_2). HRESIMS calcd for $C_{10}H_{12}N_2O_3ClS_2$ $(M+H)^+$ 306.9972, found: *m/z* 306.9973.

*1-(2-Chloro-4-nitro-5-vinylsulfathien-3-yl)-2,6-dimethylpiperidine (**4k**)*. Yield: 60%. Viscous oil. R_f = 0.70 (ether : petrol ether = 1:3). IR (film): 2967, 2930, 1538 (NO_2), 1492, 1453, 1327 (NO_2), 1118, 1027, 958, 839, 793, 720 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.56 m (1H, C_6-H), 5.87 m (2H, C_7-H), 3.28 br s (total 2H, NCH), 1.62 m (total 4H, CH_2), 1.32 m (2H, CH_2), 0.80 d (total 6H, Me, J = 5.9 Hz). HREIMS calcd for $C_{13}H_{17}N_2O_2ClS_2$ 332.0420, found: *m/z* 332.0420.

8-(2-Chloro-4-nitro-5-vinylsulfathien-3-yl)-1,4-dioxa-8-azaspiro[4.5]decane ***(4l).*** Yield: 88%, mp 53-55°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2966, 2859, 1542 (NO_2), 1486, 1461, 1312 (NO_2), 1221, 1139, 1105, 1048, 951, 903, 815, 760, 727 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.54 dd (1H, C_6-H, J = 16.4, 9.2 Hz, $^1J_{C,H}$ = 176 Hz), 5.86 d (1H, C_7-H_{trans}, J = 16.4 Hz, $^1J_{C,H}$ = 160 Hz), 5.81 d (1H, C_7-H_{cis}, J = 9.2 Hz, $^1J_{C,H}$ = 162 Hz), 3.99 br s (total 4H, OCH_2, $^1J_{C,H}$ = 149 Hz), 3.27 m (total 4H, NCH_2, $^1J_{C,H}$ = 139 Hz), 1.83 m (total 4H, CCH_2, $^1J_{C,H}$ = 129 Hz). MS: *m/z* 362 [M^+]. ***Anal.*** Calcd for $C_{13}H_{15}N_2O_4ClS_2$: C, 43.03; H, 4.17; N, 7.72; Cl, 9.77; S, 17.67. Found: C, 42.96; H, 4.18; N, 7.92; Cl, 9.77; S, 17.58.

2-Chloro-3-(4-benzylpiperaz-1-yl)-4-nitro-5-vinylsulfanylthiophene ***(4m)***. Yield: 60%, mp 107-109°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2987, 2854, 1545 (NO_2), 1453, 1273 (NO_2), 957, 877, 760, 701 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 7.66 m (1H, Ph), 7.45 m (4H, Ph), 6.81 dd (1H, C_6-H, J = 16.2, 9.2 Hz), 5.99 d (1H, C_7-H_{trans}, J = 16.2 Hz), 5.97 d (1H, C_7-H_{cis}, J = 9.2 Hz), 4.39 br s (2H, NCH_2Ph), 3.72 m (2H, NCH_2), 3.29 br s (total 4H, NCH_2), 3.09 br s (2H, NCH_2). HREIMS calcd for $C_{17}H_{18}N_3O_2ClS_2$ 395.0529, found: *m/z* 395.0529.

2-Chloro-3-(4-(3-chlorophenyl)piperaz-1-yl)-4-nitro-5-vinylsulfanylthiophene ***(4n)***. Yield: 80%, mp 63-64°C (petrol ether : dichloromethane = 1 : 1). IR (KBr): 2959, 2839, 1594, 1542 (NO_2), 1487, 1322 (NO_2), 1235, 1144, 988, 942, 760, 725 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 7.18 dd (1H, Ph, J = 8.1, 7.7 Hz), 6.93 m (1H, Ph), 6.84 d (1H, Ph, J = 7.7 Hz), 6.83 d (1H, Ph, J = 8.1 Hz), 6.54 dd (1H, C_6-H, J = 16.4, 9.3 Hz), 5.89 d (1H, C_7-H_{trans}, J = 16.4 Hz), 5.83 d (1H, C_7-H_{cis}, J = 9.2 Hz), 3.32 m (total 8H, NCH_2). MS: *m/z* 415 [M^+]. ***Anal.*** Calcd for $C_{16}H_{15}N_3O_2Cl_2S_2$: C, 46.16; H, 3.63; N, 10.09; Cl, 17.03; S, 15.40. Found: C, 45.34; H, 3.64; N, 10.27; Cl, 17.01; S, 15.40.

1,4-Bis-[2,2-dichloro-1-([1,3]dithiolan-2-ylidene-nitromethyl)vinyl]piperazine ***(5)***. (General Procedure A). Reaction time: 10 h at 40-45°C. Yield: 50%, mp 212-215°C (MeOH : dichloromethane = 1 : 2). IR (KBr): 2953, 2847, 1566, 1516, 1455, 1373, 1278, 1134, 1023, 988, 776, 704 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.69 br s (total 8H, SCH_2), 2.99 br s (total 8H, NCH_2). ^{13}C-NMR: 174.5, 139.7, 129.1, 110.9, 49.3 (NCH_2), 40.4, 38.2 (SCH_2). HREIMS calcd for $C_{16}H_{16}N_4O_4Cl_4S_4$ 595.8809, found: *m/z* 595.8809.

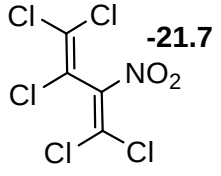
1,4-Bis-(2-chloro-4-nitro-5-vinylsulfanyl-thien-3-yl)piperazine ***(6).*** (General Procedure B). Reaction time: 10 h at 20-25°C. Yield: 82%, mp 177-179°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2949, 2889, 2850, 1590, 1536, 1485, 1372, 1329, 1175, 992, 756, 723 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 6.55 dd (2H, CH_2=C<u>H</u>, J = 16.3, 9.3 Hz), 5.87 d (2H, C<u>H</u>$_{2,trans}$=CH, J = 16.3 Hz), 5.81 d (2H, C<u>H</u>$_{2,cis}$=CH, J = 9.3 Hz), 3.30 br s (8H,

NCH_2). ^{13}C-NMR: 141.3 ($\underline{C}NCH_2$), 140.5 (S-C-S), 139.6 (CNO_2), 126.9 (CH_2=$\underline{C}$H), 125.9 ($\underline{C}H_2$=CH), 119.0 (CCl), 50.9 (NCH_2). MS: *m/z* 524 [M^+]. HREIMS calcd for $C_{16}H_{14}N_4O_4Cl_2S_4$ 523.9275, found: *m/z* 523.9275.

*1,4-Bis-(2-chloro-5-vinylsulfinyl-4-nitrothien-3-yl)piperazine (**7**)*. 0.53 g (1.00 mmol) of the thiophene (**6**) in 30 mL of dichloromethane and 0.36 g (2.10 mmol) of *m*-CPBA were stirred for 1 h at –10°C and additional 24 h at rt. After evaporation of the solvent 20 mL of methanol was added. The resulting mixture was neutralized with aqueous sodium hydroxide (10%) and stirred for 1 h at rt. The precipitated, red to orange solid was isolated and subsequently washed with water and cold methanol (0.39 g, 70%); mp 130-132°C (petrol ether : chloroform = 1 : 2). IR (KBr): 2956, 2850, 1546, 1504, 1435, 1334, 1173, 1072, 959, 758, 655 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): 7.09 dd (2H, CH_2=C$\underline{H}$, *J* = 16.3, 9.5 Hz), 6.37 dd (2H, C$\underline{H}_{2,trans}$=CH, *J* = 16.3, 1.0 Hz), 6.07 dd (2H, C$\underline{H}_{2,cis}$=CH, *J* = 9.5, 1.0 Hz), 3.36 m (total 8H, NCH_2). ^{13}C-NMR: 152.3 (S-C-S), 141.7 ($\underline{C}NCH_2$), 139.6 (CH_2=$\underline{C}$H), 139.4 (CNO_2), 126.5 (CCl), 122.7 ($\underline{C}H_2$=CH), 50.8 (N$\underline{C}H_2$). MS: *m/z* 556 [M^+]. HREIMS calcd for $C_{16}H_{14}N_4O_6Cl_2S_4$ 555.9173, found: *m/z* 555.9173.

In addition, some representative compounds were further characterized by N-NMR. Usually, nitro-groups were unambiguously detectable as broadened singlets by ^{14}N-NMR (≤512 scans) inspite of quadrupole relaxation, whereas amino groups had to be assigned using the ^{15}N resonance.[42] In most cases, the latter method required 16 k FID scans with inverse-gated decoupling.

N-NMR spectral data of 3-amino-4-nitrothiophene (**4g**) and different precursors



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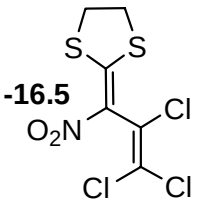
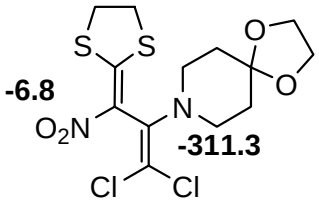
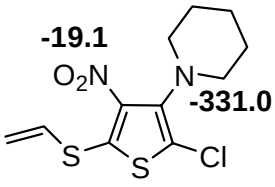


2



3l



4g

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25. X-Ray Diffraction Analysis of $C_{10}H_{11}N_2O_3ClS_2$: A clear-transparent orange crystal (from petrol ether), crystal size 0.2 × 0.2 × 0.1 mm, was measured at a temperature of 223(2) K by using a STOE IPDS II diffractometer with Mo-K_α radiation (λ = 0.71073 Å) and a graphite monochromator. 15271 reflections were collected in the range $2.63° \le \vartheta \le 23.39°$; h,k,l range from –12, –17, –16 to 11, 17, 15. Crystal system: orthorhombic, space group Pbca (No. 61), Z = 8, a = 11.0936(15) pm , b = 15.518(3) pm, c = 15.037(2) pm, V_{EZ} = 2588.5(8) 10^6 pm^3; D_{calc} = 1.574 g cm^{-3}; μ (Mo-K_α) = 0,618 mm^{-1}. The structure was solved by direct methods (SHELXS-97[a]) using 1868 independent reflections. Structure refinement: Full matrix least-squares methods on F^2 using SHELXL-97[b] all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms were taken from a difference fourier synthesis and isotropically refined. The refinement converged to a final $wR_2 = 0.0911$ for 1868 unique reflections and $R_1 = 0.0403$ for 1336 observed reflections [$I_o > 2\sigma(I_o)$] and 207 refined parameters with a goodness-of-fit of 1.034. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-227350. 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, e-mail: deposit@ccdc.cam.ac.uk).

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