Chemistry of Polyhalogenated Nitrobutadienes, Part 11: *ipso*-Formylation of 2-Chlorothiophenes under Vilsmeier-Haack Conditions

Eva-Janina Vogt, Viktor A. Zapol'skii, Eva Nutz, and Dieter E. Kaufmann

Institute of Organic Chemistry, Clausthal University of Technology, Leibnizstraße 6, 38678 Clausthal-Zellerfeld, Germany

Reprint requests to Prof. Dr. D. E. Kaufmann. Fax: +49-5323-722834.
E-mail: dieter.kaufmann@tu-clausthal.de

Z. Naturforsch. **2012**, *67b,* 285 – 294; received March 2, 2012

The regioselective *ipso*-formylation of electron-rich, 3,4-push-pull-substituted 2-chlorothiophenes under Vilsmeier-Haack conditions was performed in good yields. The synthetic scope of this new reaction was explored using various halothiophenes, chloroanilines, and 1-methyl-3-chloroindole. In comparison with their structural C-H analogs the chlorinated thiophenes, anilines, and the indole proved to be less reactive toward electrophilic attack by chloromethyleniminium salts.

Key words: Vilsmeier-Haack Formylation, Thiophene, Push-Pull Substitution, *ipso*-Substitution, Enamine

Introduction

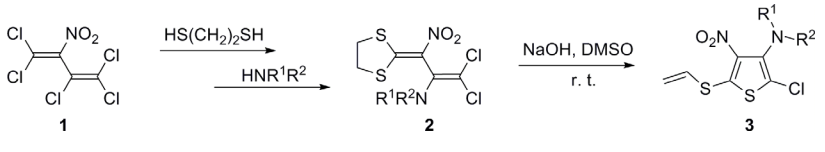
Within our scope to employ 2-nitroperchlorobutadiene (**1**) as a versatile building block for the predictable synthesis of bioactive heterocycles [1a – d], we have also developed an efficient three-step synthesis of the 3-amino-4-nitrothiophenes **3** *via* the aminodithiolanes **2** [1d] (Scheme 1).

These thiophenes have a unique substitution pattern and are interesting precursors for thiophene-based optoelectronic materials [2] such as conducting polymers with small HOMO-LUMO gaps. To interconnect these thiophene monomers *via* π bonds, introduction of a formyl group in 2-position of **3** was intended. The Vilsmeier reaction is known to place a formyl group regioselectively onto activated heteroaromatic ring systems such as thiophenes [3]. As a primary selective reduction of the C-Cl group proved difficult, it was aimed to *ipso*-substitute this position directly. Gratifyingly, this formylation was successful. Therefore, in the present paper we have focused our efforts on the synthetic scope of the *ipso*-substitution of substituted 2-halothiophenes.

Results and Discussion

The Vilsmeier reaction comprises the selective electrophilic substitution of activated C-H aromatic or heteroaromatic ring systems with *N*-derivatives of the unstable formyl chloride – chloromethyleniminium salts – being formed by reaction of *N*,*N*-dimethylformamide (DMF) or *N*-methylformanilide with acid chlorides such as phosphoryl chloride or phosgene [3]. So far, *ipso*-variants of the Vilsmeier-Haack formylation have been reported rarely, either with phenylmercury compounds [4] or with *tert*-butylcalix[4]arene [5].

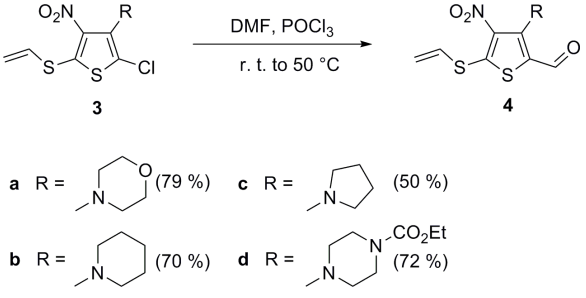
Starting from 2-nitroperchlorobutadiene (**1**) [6], the *N*-(2-chloro-4-nitro-5-(vinylsulfanyl)-thien-3-yl)-amines **3a** – **d** are accessible in very good yields (90 – 95 %) [1d]. Surprisingly, these persubstituted thiophene derivatives reacted in an S_EAr reaction with a Vilsmeier reagent under exclusive formylation at C-2, with substitution of the chloro substituent (Scheme 2). DMF or *N*-methylformanilide were used in excess as both, reactant and solvent. Phosphoryl chloride was added at 0 °C in a small excess of 10 – 20 %, and the



Scheme 1. Three-step synthesis of the 3-amino-4-nitrothiophenes **3**.

Entry	Starting material	Solvent	$POCl_3$ (eq.)	*T* (°C)	Reaction time (h)	Product	Yield (%)
1	**3a**	DMF	1.1	50	2	**4a**	79
2	**3a**	Ph(Me)NCHO	1.1	r. t.	5	**4a**	61
3	**3b**	DMF	1.2	r. t.	4	**4b**	70
4	**3c**	DMF	1.2	r. t.	3	**4c**	50
5	**3d**	DMF	1.2	50	5	**4d**	72

Table 1. Reaction conditions for the *ipso*-formylation of 2-chlorothiophenes **3**.

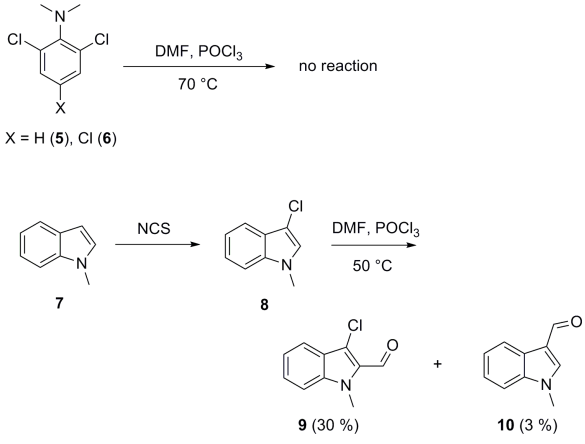


Scheme 2. Vilsmeier-Haack *ipso*-formylation of the persubstituted 2-chlorothiophenes **3**.

temperature was slowly raised, first to room temperature (r. t.), and then to 50 °C. The resulting aldehydes **4a** – **d** were obtained in moderate to good yields (50 – 79 %, Table 1), without a reaction of the vinylsulfanyl group.

The substitution pattern of the tetrasubstituted thiophenes **3** is unique, comprising a combination of a chloroenamine, a push-pull system and an aminothioketenacetal, all in one leading to a very electron-rich molecule. This special electronic situation should facilitate an electrophilic attack at C-2. Although the mechanism of this new reaction is not yet fully understood [7], we became interested in its synthetic scope and limitations, the essential substitution pattern as well as the specific reaction conditions. Therefore, under the same reaction conditions we reacted aromatic haloenamines such as 2,6-dichloro-*N*,*N*-dimethylaniline (**5**) and 2,4,6-trichloro-*N*,*N*-dimethylaniline (**6**) which were synthesized according to the literature [8]. Both chloroanilines proved to be not reactive enough to get formylated, neither at 50 °C nor at 70 °C (Scheme 3).

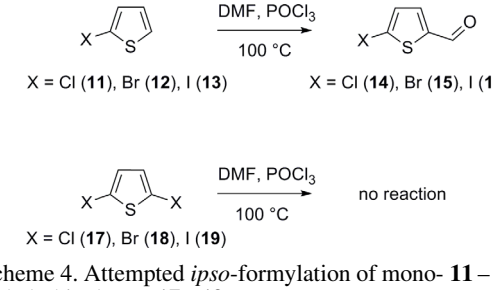
Indoles are known to be easily attacked at C-3, even by rather weak electrophiles such as Mannich and Vilsmeier reagents. The *N*-heteroaromatic haloenamine 3-chloro-1-methyl-1*H*-indole (**8**) [9], though, at 50 °C and with 1.1 eq. of phosphoryl chloride and an excess of DMF, afforded 3-chloro-1-methyl-1*H*-indole-2-carbaldehyde (**9**) as the main product with 30 % yield. In accordance with the literature, C-2 is formylated in a Vilsmeier reaction, when the other-



Scheme 3. Attempted *ipso*-formylation of chloroanilines **5** and **6** and chloroindole **8**.

wise preferred C-3 position is blocked by a chlorine substituent [10]. However, 1-methyl-1*H*-indole-3-carbaldehyde (**10**) was found as a by-product with 3 % yield showing that the *ipso*-Vilsmeier reaction found for the thiophenes **3a** – **d** is transferable to other systems (Scheme 3).

In the next step we investigated the influence of the thiophene ring and its substitution pattern on the formylation reaction of different halogenated thiophenes. Under Vilsmeier-Haack conditions with 2.2 eq. of phosphoryl chloride at 50 °C up to 100 °C the 2-halothiophenes (Cl **11**, Br **12**, I **13**) afforded the classical Vilsmeier reaction products exclusively, *viz.* the 5-halo-2-thiophenecarbaldehydes (Cl **14**, Br **15**, I **16**); with 2,5-dihalothiophenes (Cl **17**, Br **18**, I **19**) under the same conditions no reaction occurred (Scheme 4).



Scheme 4. Attempted *ipso*-formylation of mono- **11** – **13** and di-halothiophenes **17** – **19**.

Entry	Starting material	Solvent	$POCl_3$ (eq.)	*T* (°C)	Reaction time (h)	Product	Yield (%)
1	**20**	DMF	1.1	50	1.5	**21**	62
2	**22**	DMF	1.1	r. t., 50	1.5	–	–
3	**23**	DMF	1.1	50	4.5	**21**	25
4	**24**	DMF	1.1	50	1.0	**25**	33

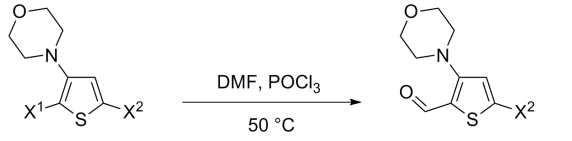
Table 2. Reaction conditions for the *ipso*-formylation of 3-morpholinothiophenes **20** and **22** – **24**.

Entry	Starting material	Solvent	$POCl_3$ (eq.)	*T* (°C)	Reaction time (h)	Product	Yield (%)
1	**26**	DMF	1.1	50	1.5	**27**	83
2	**28**	DMF	1.1	50	24	**30**, **31** (0.32 : 1)	66
3	**29**	DMF	1.1	50	3.0	**30**, **31** (1 : 0.22)	84

Table 3. Reaction conditions for the *ipso*-formylation of 3,4-ethylenedioxythiophenes **26**, **28** and **29**.

In accordance with the literature [10 – 13] the halogen substituents deactivate the thiophene so that the reactions require higher temperatures (100 °C) to take place. In both cases the halogen atoms act as protecting substituents for the 2- or 2,5-position and, additionally in case of bromine and iodine substituents, they were exchanged by chlorine to a large extent. The exchange mechanism is yet not fully understood.

Since the halothiophenes **11** – **13** and **17** – **19** did not react by *ipso*-substitution of the halogen while both, the 3-chloroindole **8**, which reacted to the 3-carbaldehyde **10** at least partially, as well as the aminonitrothiophenes **3** show this new reaction, apparently either an amino group or more general +M substituents facilitate this formylation reaction. Therefore, a number of 3-morpholinothiophenes were chosen as test compounds which were among the most stable ones in the series of **3a** – **d**. For comparison, 4-(3-thienyl)morpholine (**20**), which was synthesized by a Buchwald-Hartwig reaction [15], was formylated in a Vilsmeier reaction, affording thiophene-2-carbaldehyde **21** regioselectively with 62 % yield. The halogenated analogs 4-(2-chloro-3-thienyl)morpholine (**22**) and 4-(2-bromo-3-thienyl)morpholine (**23**) were synthesized from **20** with NCS and NBS in DMF. 4-(2,5-Dichloro-3-thienyl)morpholine (**24**) was synthesized from 3-bromo-2,5-dichlorothiophene according to Buchwald *et al.* [15]. All of these aminohalothiophenes are rather unstable, and it is not possible to store them over a long period of time. They were tested under Vilsmeier-Haack conditions with 1.1 eq. of phosphoryl chloride at r. t. to 50 °C (Scheme 5, Table 2). In the case of chlorothiophene **22** no product could be isolated but instead decomposition took place. When reacting bromothiophene **23**, thiophene-2-carbaldehyde **21** was obtained with 25 % yield as the only product. Although C-5 was not blocked by an additional substituent, the reaction occurred at C-2



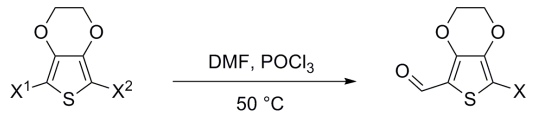
20 $X^1 = X^2 = H$
22 $X^1 = Cl$, $X^2 = H$
23 $X^1 = Br$, $X^2 = H$
24 $X^1 = X^2 = Cl$

21 $X^2 = H$ (25–62 %)
25 $X^2 = Cl$ (33 %)

Scheme 5. Attempted *ipso*-formylation of 3-morpholinothiophenes **20** and **22** – **24**.

next to the activating morpholino group in an *ipso*-substitution of the bromo substituent. The dichlorothiophene **24** reacted in the same way at the activated C-2 position to give the thiophene-2-carbaldehyde **25** with 33 % yield.

The 3-amino-4-nitro substitution of thiophenes **3a** – **d** is a valuable tool for the construction of new conducting polymers. Therefore a comparison of their reactivity towards Vilsmeier reagents with the 3,4-bisalk-oxy-substituted ethylenedioxythiophene (EDOT, **26**), the monomer of the most important conducting polymer polyethylenedioxythiophene (PEDOT) [16], is most interesting. The EDOT was used in classical Vilsmeier reactions and afforded as expected the 3,4-ethylenedioxythiophene-2-carbaldehyde (**27**) in good yield (83 %). For comparison, 2,5-dibromo-3,4-ethylenedioxythiophene (**28**), which was synthesized according to the literature [18], and 2-bromo-3,4-ethylenedioxythiophene (**29**), which was synthesized under similar conditions with NBS in DMF, were reacted under Vilsmeier-Haack conditions with 1.1 eq. of phosphoryl chloride at 50 °C (Scheme 6, Table 3). Starting with **28** the same reaction as with the thiophenes **3a** – **d** took place resulting in the *ipso*-substitution of a bromo substituent by a formyl group. 5-Bromo-3,4-ethylenedioxythiophene-2-carbaldehyde (**30**) and 5-chloro-3,4-ethylenedioxythiophene-2-carbaldehyde (**31**) were ob-



26 $X^1 = X^2 = H$
28 $X^1 = X^2 = Br$
29 X^1 = H, X^2 = Br

27 X = H
30 X = Br
31 X = Cl

Scheme 6. *ipso*-Formylation of 3,4-ethylenedioxythiophenes **26**, **28** and **29**.

tained as a mixture (0.32 : 1) with 66 % yield. This result shows that alkoxy substituents at C-3 also facilitate an *ipso*-Vilsmeier attack at position C-2. At C-5 the bromo substituent is exchanged by a chlorine atom of the phosphoryl chloride to a large extent, probably by an addition/elimination mechanism. In comparison, the reaction of **29** gave the same product mixture of **30** and **31** (1 : 0.22) with 84 % yield. In an intramolecular competition, both C-2 and C-5 have the +M alkoxy substituent in α-position, but the reaction only takes place at C-5 in a classical Vilsmeier reaction to give the aldehydes **30** and **31**. The bromine substituent at C-2 serves as a protecting group and is only exchanged by chlorine to a lesser extent.

Conclusion

A new and unexpected variant of the *ipso*-Vilsmeier reaction has been found in which a halogen is substituted by a formyl group under Vilsmeier conditions. This reaction was first developed with electron-rich thiophenes **3a** – **d**, featuring a unique substitution pattern. In the present paper the synthetic scope of this reaction was examined. Aromatic chloroenamines such as the haloanilines **5** and **6** either did not react in this manner or only in a side reaction, like the 3-chloroindole **8**. Thiophenes, though bearing an activating +M substituent in 3-position, show this *ipso*-substitution at C-2, even if C-5 remains unsubstituted such as in 4-(2-bromo-3-thienyl)morpholine (**23**). In case of an intramolecular competition between an equally activated C-H and C-Br bond, formylation of the C-H bond is preferred. So far, this new reaction is limited to +M-activated 2- or 2,5-halothiophenes. In the near future we will try to gain further insight into the mechanism of this reaction type.

Experimental Section

Melting points were determined with a Differential Scanning Calorimeter Perkin Elmer DSC6. Thin layer chromatography (TLC) was performed on Merck TLC-plates (aluminum based) silica gel 60 F 254. FT-IR spectra were obtained with a Bruker Vector 22 FT-IR spectrometer in the range of 700 to 4000 cm^{-1} (2.5 % pellets in KBr). Mass spectra were obtained on a Varian 320 MS Triple Quad GC/MS/MS instrument with a Varian 450-GC unit usually in direct mode with electron impact (70 eV). In the case of chlorinated and brominated compounds, all peak values of molecular ions as well as fragments refer to the isotopes ^{35}Cl and ^{79}Br. The elemental composition was confirmed either by combustion analysis or by high-resolution EI and (+)-ESI mass spectrometry. All HRMS results were satisfactory in comparison to the calculated accurate masses of the molecular ions (±2 ppm, R ∼ 10000). ^1H NMR (600 MHz), ^{13}C NMR (150 MHz): Avance III 600 MHz FT-NMR spectrometer (Bruker, Rheinstetten, Germany); ^1H NMR (400 MHz), ^{13}C NMR (100 MHz): Avance 400 FT-NMR spectrometer (also Bruker). ^1H NMR (200 MHz), ^{13}C NMR (50 MHz): DPX 200 FT-NMR spectrometer (also Bruker). ^1H and ^{13}C NMR spectra were referenced to the residual solvent peak: $CDCl_3$, δ = 7.26 (^1H), δ = 77.0 (^{13}C) ppm. Chemical shifts δ are given in ppm. In most cases, peak assignments were accomplished by HSQC and HMBC NMR experiments. Purifications were carried out by means of column chromatography on silica gel 60 (Merck). Petroleum ether as eluent had the boiling range 60 – 70 °C.

*Ethyl 4-(1,1-dichloro-3-(1,3-dithiolan-2-ylidene)-3-nitro-1-propen-2-yl)-1-piperazinecarboxylate (**2d**)*

2d was synthesized as reported for the dithiolanes **2a** – **c** [1d]. At r. t. ethyl 1-piperazinecarboxylate hydrochloride (1.60 g, 10.20 mmol) was added to a solution of 2-(2,3,3-trichloro-1-nitro-2-propen-1-ylidene)-1,3-dithiolane (1.00 g, 3.40 mmol) and triethylamine (1.03 g, 10.20 mmol) in methanol (15 mL). The mixture was refluxed for 3 d. After cooling to r. t. the solution was concentrated *in vacuo* to 40 % of its volume. Water (5 mL) was added, and the resulting solid was filtered, washed with water (3 × 10 mL) and dried *in vacuo*. The product was isolated as a red solid; yield: 1.33 g (95 %), m. p. 59 °C. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.1 Hz, 3 H, CH_3), 2.98 (bs, 4 H, CH_2NCH_2), 3.46 – 3.64 (m, 8 H, CH_2NCH_2 + $S(CH_2)_2S$), 4.13 (q, J = 7.1 Hz, 2 H, CH_2). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.6 (1 C, CH_3), 37.6 (1 C, SCH_2), 40.1 (1 C, SCH_2), 43.8 (1 C, CH_2), 49.1 (2 C, CH_2NCH_2), 61.4 (2 C, CH_2NCH_2), 114.1 (1 C, CCl_2), 130.5 (1 C, C-NO_2), 139.0 (1 C, C-$(N(CH_2)_2)$), 155.3 (1 C, COO), 170.7 (1 C, SCS). – IR (KBr): ν = 2980, 2906, 2845, 2605, 2498, 1696, 1584, 1522, 1461, 1431, 1383, 1346, 1295, 1276, 1248, 1136, 1118, 1074, 1022, 989, 949, 912, 850, 799, 775, 711 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 414 (27) $[M+H]^+$, 350 (37), 285 (49), 210 (77), 130 (88), 105 (46), 70 (64), 56 (100). – HRMS ((+)-ESI): m/z = 414.0114 (calcd. 414.0116 for $C_{13}H_{18}Cl_2N_3O_4S_2$, $[M+H]^+$).

*Ethyl 4-(2-chloro-4-nitro-5-(vinylsulfanyl)-3-thienyl)-1-piperazinecarboxylate (**3d**)*

3d was synthesized according to the literature [1d]. An aqueous (aq.) solution of NaOH (40 %, 1.00 g, 10.0 mmol) was added to a solution of ethyl 4-(1,1-dichloro-3-(1,3-dithiolan-2-ylidene)-3-nitro-1-propen-2-yl)-1-piperazinecarboxylate (**2d**) (826 mg, 2.00 mmol) in DMSO (10 mL) at 0 °C within 10 min. After 1 h at 0 °C the mixture was stirred for an additional 3 h at r. t. Then cold water (70 mL) was added at 0 to 5 °C. The mixture was acidified to pH = 1 upon dropwise addition of conc. aq. HCl. The product precipitated as an oil, and the aq. fraction was decanted. The oily product was dissolved in chloroform (50 mL), the solution was washed with aq. HCl (15 %, 3 × 30 mL) and water (2 × 30 mL), and was then dried (sodium sulfate). The solvent was evaporated and the product isolated as an orange solid; yield: 679 mg (90 %), m. p. 109 °C. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 3.11 – 3.17 (m, 4 H, CH_2NCH_2), 3.54 – 3.59 (m, 4 H, CH_2NCH_2), 4.14 (q, J = 7.1 Hz, 2 H, CH_2), 5.82 (d, J = 9.2 Hz, 1 H, SCHC$H_{2,cis}$), 5.87 (d, J = 16.4 Hz, 1 H, SCHC$H_{2,trans}$), 6.52 (dd, J = 16.4, 9.2 Hz, 1 H, SCH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.6 (1 C, CH_3), 44.4 (2 C, CH_2NCH_2), 49.9 (2 C, CH_2NCH_2), 61.4 (1 C, CH_2), 119.5 (1 C, *C*-Cl), 126.4 (1 C, SCH*C*H_2), 126.6 (1 C, S*C*H), 139.2 (1 C, *C*-NO_2), 140.9 (1 C, *C*-(N(CH_2)$_2$)), 141.2 (1 C, *C*-SCH) 155.5 (1 C, *C*OO). – IR (KBr): ν = 2977, 2959, 2899, 2850, 1699, 1590, 1546, 1484, 1471, 1426, 1384, 1357, 1327, 1278, 1244, 1222, 1172, 1119, 1082, 1053, 1032, 994, 972, 933, 874, 830, 813, 767, 719 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 376 (16) $[M]^+$, 258 (10), 233 (16), 217 (18), 195 (17), 181 (14), 144 (24), 130 (13), 116 (40), 103 (18), 83 (91), 72 (44), 56 (100). – $C_{13}H_{16}ClN_3O_4S_2$ (377.87): calcd. C 41.32, H 4.27, N 11.12, S 16.97, Cl 9.38; found C 41.63, H 4.23, N 11.10, S 17.05, Cl 9.40.

General procedure for all formylation reactions under Vilsmeier-Haack conditions

To a solution of the starting material in anhydrous DMF or dimethylformanilide under an atmosphere of nitrogen and at 0 °C, 1.1 – 2.2 eq. of phosphoryl chloride ($POCl_3$) was added slowly by a syringe. The solution was then heated to a temperature between r. t. and 100 °C for 1 – 24 h (TLC control) under stirring. After cooling to r. t. the reaction mixture was poured into ice water and stirred for 10 min. In case of the morpholino derivative **4a** in DMF the precipitate was filtered, washed with water (3 × 20 mL), dried *in vacuo* and purified by column chromatography. In general, for the aminonitrothiophenes **4a** – **d** the aq. fraction was extracted with ethyl acetate (3×), and the organic fraction was dried (magnesium sulfate). After evaporation of the solvent the product was purified by column chromatography. In all other cases a sat. aq. solution of sodium hydrogen carbonate was added. The mixture was stirred for 1 h and extracted with dichloromethane (3×). The organic fraction was dried (magnesium sulfate). After evaporation of the solvent the products were purified by column chromatography.

*3-(4-Morpholino)-4-nitro-5-(vinylsulfanyl)thiophene-2-carbaldehyde (**4a**)*

Method I: The product was synthesized according to the general procedure from 4-(2-chloro-4-nitro-5-(vinylsulfanyl)-3-thienyl)morpholine (**3a**) (2.50 g, 8.2 mmol), anhydrous DMF (15 mL), and 1.1 eq. of $POCl_3$ (0.82 mL, 9.0 mmol); 50 °C, 2 h, ice water (110 mL); column chromatography (petroleum ether-ethyl acetate 3 : 1). The product was isolated as an orange solid; yield: 1.944 g (79 %).

Method II: The product was synthesized according to the general procedure from 4-(2-chloro-4-nitro-5-(vinylsulfanyl)-3-thienyl)morpholine (**3a**) (100 mg, 0.327 mmol), dimethylformanilide (1 mL), and 1.1 eq. of $POCl_3$ (0.033 mL, 0.360 mmol); r. t., 5 h, ice water (5 mL), ethyl acetate (3 × 15 mL); column chromatography (petroleum ether-ethyl acetate 4 : 1). The product was isolated as an orange solid; yield 59 mg (61 %), m. p. 155 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.39 – 3.41 (m, 4 H, CH_2NCH_2), 3.88 – 3.90 (m, 4 H, CH_2OCH_2), 5.99 (d, J = 9.2 Hz, 1 H, SCHC$H_{2,cis}$), 6.02 (d, J = 16.4 Hz, 1 H, SCHC$H_{2,trans}$), 6.65 (dd, J = 16.4, 9.2 Hz, 1 H, SCH), 10.01 (s, 1 H, CHO). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.6 (2 C, CH_2NCH_2), 66.7 (2 C, CH_2OCH_2), 124.5 (1 C, *C*-CHO), 125.4 (1 C, S*C*H), 128.7 (1 C, SCH*C*H_2), 136.0 (1 C, *C*-NO_2), 150.3 (1 C, *C*-(N(CH_2)$_2$)), 159.8 (1 C, *C*-SCH), 180.1 (1 C, *C*HO). – IR (KBr): ν = 2972, 2872, 1624, 1533, 1490, 1446, 1424, 1376, 1352, 1332, 1304, 1264, 1223, 1137, 1111, 1067, 1021, 996, 965, 951, 867, 848, 824, 783, 758, 713 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 301 (3) $[M]^+$, 283 (6) $[M–O]^+$, 265 (14), 237 (14), 227 (19), 211 (13), 197 (10), 183 (11), 168 (15), 155 (19), 137 (17), 123 (18), 112 (38), 95 (47), 73 (100), 84 (35), 69 (100), 59 (56). – HRMS (EI): m/z = 300.0235 (calcd. 300.0239 for $C_{11}H_{12}N_2O_4S_2$, $[M]^+$).

*4-Nitro-3-(1-piperidinyl)-5-(vinylsulfanyl)thiophene-2-carbaldehyde (**4b**)*

The product was synthesized according to the general procedure from 4-(2-chloro-4-nitro-5-(vinylsulfanyl)-3-thienyl)piperidine (**3b**) (608 mg, 2.0 mmol), anhydrous DMF (4 mL), and 1.2 eq. of $POCl_3$ (0.22 mL, 2.4 mmol); r. t., 4 h, ice water (5 mL), ethyl acetate (3 × 30 mL); column chromatography (petroleum ether-ethyl acetate 1 : 1). The product was isolated as a red solid; yield: 417 mg (70 %), m. p. 133 °C. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60 – 1.83 (m, 6 H, (CH_2)$_3$), 3.30 – 3.35 (m, 4 H, CH_2NCH_2), 5.94 (d,

J = 9.2 Hz, 1 H, SCHC$H_{2,cis}$), 5.98 (d, J = 16.4 Hz, 1 H, SCHC$H_{2,trans}$), 6.65 (dd, J = 16.4, 9.2 Hz, 1 H, SCH), 9.97 (s, 1 H, CHO). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.6 (1 C, CH_2), 25.9 (2 C, CH_2), 55.1 (2 C, CH_2NCH_2), 122.9 (1 C, C−CHO), 125.7 (1 C, SCH), 128.2 (1 C, SCHCH_2), 136.0 (1 C, C-NO_2), 151.9 (1 C, C-(N$(CH_2)_2$)), 159.1 (1 C, C-SCH), 180.1 (1 C, CHO). – IR (KBr): ν = 3088, 3002, 2952, 2939, 2921, 2846, 1617, 1531, 1486, 1462, 1443, 1423, 1374, 1352, 1342, 1309, 1277, 1228, 1159, 1149, 1103, 1045, 995, 966, 942, 915, 859, 813, 776, 760, 713 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 299 (38) [M+H]$^+$, 281 (44), 263 (100), 250 (24), 237 (62), 224 (23), 209 (40), 199 (28), 183 (25), 164 (29), 150 (21), 136 (22), 123 (20), 112 (32), 96 (39), 84 (42), 69 (68), 55 (64). – HRMS (EI): m/z = 298.0500 (calcd. 298.0446 for $C_{12}H_{14}N_2O_3S_2$, [M]$^+$).

*4-Nitro-3-(1-pyrrolidinyl)-5-(vinylsulfanyl)thiophene-2-carbaldehyde (**4c**)*

The product was synthesized according to the general procedure from 4-(2-chloro-4-nitro-5-(vinylsulfanyl)-3-thienyl)pyrrolidine (**3c**) (580 mg, 2.0 mmol), anhydrous DMF (4 mL), and 1.2 eq. of $POCl_3$ (0.22 mL, 2.4 mmol); r. t., 4 h, ice water (5 mL), ethyl acetate (3 × 30 mL); column chromatography (petroleum ether-ethyl acetate 1 : 1). The product was isolated as a red-brown solid; yield: 284 mg (50 %), m. p. 161 °C. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.04 – 2.10 (m, 6 H, (CH_2)$_2$), 3.40 – 3.47 (m, 4 H, CH_2NCH_2), 5.91 (d, J = 9.2 Hz, 1 H, SCHC$H_{2,cis}$), 5.95 (d, J = 16.4 Hz, 1 H, SCHC$H_{2,trans}$), 6.65 (dd, J = 16.4, 9.2 Hz, 1 H, SCH), 9.72 (s, 1 H, CHO). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.0 (2 C, (CH_2)$_2$), 54.8 (2 C, CH_2NCH_2), 117.5 (1 C, C−CHO), 125.3 (1 C, SCH), 127.8 (1 C, SCHCH_2), 145.5 (1 C, C-NO_2), 157.3 (1 C, C-SCH), 162.7 (1 C, C-(N$(CH_2)_2$)), 180.1 (1 C, CHO). – IR (KBr): ν = 3088, 3033, 2991, 2956, 2882, 2842, 1597, 1539, 1498, 1453, 1432, 1371, 1351, 1330, 1310, 1276, 1247, 1234, 1176, 1132, 1110, 1045, 1019, 966, 942, 874, 834, 795, 757, 741, 711 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 285 (3) [M+H]$^+$, 267 (16), 249 (22), 211 (12), 196 (10), 184 (20), 151 (24), 140 (18), 111 (27), 97 (48), 84 (45), 70 (100), 59 (41). – HRMS (EI): m/z = 284.0288 (calcd. 284.0289 for $C_{11}H_{12}N_2O_3S_2$, [M]$^+$).

*Ethyl 4-(2-formyl-4-nitro-5-(vinylsulfanyl)-3-thienyl)-1-piperazinecarboxylate (**4d**)*

The product was synthesized according to the general procedure from 754 mg (2.0 mmol) ethyl 4-(2-chloro-4-nitro-5-(vinylsulfanyl)-3-thienyl)-1-piperazinecarboxylate (**3d**), anhydrous DMF (4 mL), and 1.2 eq. of $POCl_3$ (0.22 mL, 2.4 mmol); 50 °C, 5 h, ice water (5 mL), ethyl acetate (3 × 30 mL); column chromatography (petroleum ether-ethyl acetate 1 : 1). The product was isolated as an orange solid; yield: 534 mg (72 %), m. p. 138 °C. – ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 3 H, CH_3), 3.33 (bs, 4 H, CH_2NCH_2), 3.67 – 3.68 (m, 4 H, CH_2NCH_2), 4.17 (q, J = 7.1 Hz, 2 H, CH_2), 5.97 (d, J = 9.1 Hz, 1 H, SCHC$H_{2,cis}$), 6.00 (d, J = 16.4 Hz, 1 H, SCHC$H_{2,trans}$), 6.63 (dd, J = 16.4, 9.1 Hz, 1 H, SCH), 9.96 (s, 1 H, CHO). – ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.6 (1 C, CH_3), 43.8 (2 C, CH_2NCH_2), 53.2 (2 C, CH_2NCH_2), 61.7 (1 C, CH_2), 125.6 (1 C, SCH), 125.6 (1 C, C−CHO), 128.8 (1 C, SCHCH_2), 136.4 (1 C, C-NO_2), 150.5 (1 C, C-(N$(CH_2)_2$)), 155.4 (1 C, COO), 159.6 (1 C, C-SCH), 180.1 (1 C, CHO). – IR (KBr): ν = 2981, 2922, 2850, 1703, 1619, 1534, 1486, 1467, 1455, 1436, 1424, 1376, 1352, 1311, 1285, 1244, 1222, 1135, 1120, 1076, 1048, 1035, 999, 969, 945, 764 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 371 (2.5) [M]$^+$, 354 (11), 336 (15), 227 (100), 210 (29), 197 (19), 183 (21), 168 (17), 155 (23), 144 (32), 130 (17), 116 (30), 97 (19). – HRMS ((+)-ESI): m/z = 394.0505 (calcd. 394.0507 for $C_{14}H_{17}N_3O_5S_2Na$, [M+Na]$^+$).

*2,6-Dichloro-N,N-dimethylaniline (**5**)*

To a solution of 2,6-dichloroaniline (1.0 g, 6.2 mmol) in toluene (10 mL) dimethyl sulfate (3.13 g, 24.5 mmol) and anhydrous potassium carbonate (858 mg, 6.2 mmol) were added, and the mixture was refluxed overnight. After cooling to r. t. aq. ammonia solution (25 %, 20 mL) was added, and the mixture was stirred for 5 min. Then ethyl acetate (20 mL) was added, the fractions were separated, and the organic fraction was washed twice with water. The product was purified by column chromatography (petroleum ether-ethyl acetate 10 : 1), then isolated as a colorless liquid; yield: 300 mg (25 %). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.89 (s, 6 H, *Me*), 6.96 (t, J = 7.8 Hz, 1 H, *H*-4), 7.25 (d, J = 7.8 Hz, 2 H, *H*-3, *H*-5). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.1 (2 C, *Me*), 125.8 (1 C, *C*-4), 129.1 (2 C, *C*-3, *C*-5), 135.5 (2 C, *C*-2, *C*-6), 146.4 (1 C, *C*-1). The NMR data were in accordance with the literature [8].

*2,4,6-Trichloro-N,N-dimethylaniline (**6**)*

2,4,6-Trichloro-*N*,*N*-dimethylaniline (**6**) was prepared according to the procedure for **5** from 2,4,6-trichloroaniline (1.0 g, 5.1 mmol), toluene (8 mL), dimethyl sulfate (2.59 g, 20.5 mmol), and anhydrous potassium carbonate (709 mg, 5.1 mmol). The product was isolated as a colorless liquid; yield: 579 mg (51 %). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (s, 6 H, *Me*), 7.27 (s, 2 H, *H*-3, *H*-5). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.0 (2 C, *Me*), 128.8 (2 C, *C*-3, *C*-5), 130.1 (1 C, *C*-4), 135.9 (2 C, *C*-2, *C*-6), 145.3 (1 C, *C*-1). The NMR data were in accordance with the literature [8].

*3-Chloro-1-methyl-1H-indole (**8**)*

3-Chloro-1-methyl-1*H*-indole (**8**) was synthesized according to the literature for the synthesis of 3-chloro-1*H*-

indole [9]. Under an atmosphere of nitrogen *N*-chlorosuccinimide (214 mg, 1.53 mmol) was added to a solution of 1-methyl-1*H*-indole (**7**) (200 mg, 1.53 mmol) in anhydrous DMF (6 mL). The reaction mixture was stirred for 2 h at r. t. in the dark, and then brine (10 mL) was added. The aq. fraction was extracted with ethyl acetate (3 × 30 mL), and the organic fraction was washed with water and dried (magnesium sulfate). After evaporation of the solvent the product was purified by column chromatography (petroleum ether-ethyl acetate 8 : 1). The product was isolated as a light-yellow oil; yield: 147 mg (58 %). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, *Me*), 7.01 (s, 1 H, NC*H*), 7.16 – 7.20 (m, 1 H, *H*-6), 7.24 – 7.31 (m, 2 H, *H*-5, *H*-7), 7.61 – 7.63 (m, 1 H, *H*-4). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.9 (1 C, *Me*), 104.4 (1 C, *C*Cl), 109.5 (1 C), 118.3 (1 C), 119.9 (1 C), 122.6 (1 C), 125.2 (1 C), 125.7 (1 C), 135.8 (1 C). – MS (EI, 70 eV): m/z (%) = 165 (100) $[M]^+$, 150 (13), 128 (13), 101 (16). The NMR data were in accordance with the literature [10].

*3-Chloro-1-methyl-1H-indole-2-carbaldehyde (**9**) / 1-methyl-1H-indole-3-carbaldehyde (**10**)*

The product was synthesized according to the general procedure from 3-chloro-1-methyl-1*H*-indole (**8**) (100 mg, 0.606 mmol), anhydrous DMF (1 mL), 1.1 eq. of $POCl_3$ (0.061 mL, 0.666 mmol); 50 °C, 3 h, ice water (5 mL), sat. aq. solution of sodium hydrogen carbonate (10 mL), CH_2Cl_2 (3 × 10 mL); column chromatography (petroleum ether-ethyl acetate 2 : 1). The products were isolated as colorless solids.

*3-Chloro-1-methyl-1H-indole-2-carbaldehyde (**9**):* yield: 35 mg (30 %), m. p. 86 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, *Me*), 7.26 – 7.32 (m, 3 H, H_{arom}), 8.25 – 8.27 (m, 1 H, H_{arom}), 10.07 (s, 1 H, C*H*O). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (1 C, *Me*), 109.4 (1 C), 112.8 (1 C), 121.2 (1 C), 123.5 (1 C), 124.0 (1 C), 124.2 (1 C), 135.9 (1 C), 136.7 (1 C), 183.8 (1 C, *C*HO). – MS (EI, 70 eV): m/z (%) = 192 (100) $[M–H]^+$, 128 (17), 101 (18). The NMR data were in accordance with the literature [10].

*1-Methyl-1H-indole-3-carbaldehyde (**10**):* yield: 3 mg (3 %), m. p. 70 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, *Me*), 7.32 – 7.38 (m, 3 H, H_{arom}), 7.69 (s, 1 H, *H*-2), 8.29 – 8.32 (m, 1 H, H_{arom}), 10.00 (s, 1 H, C*H*O). The NMR data were in accordance with the literature [10].

*5-Halo-2-thiophenecarbaldehydes **14** – **16***

The products were synthesized according to the general procedure from 2-halothiophene (3.0 mmol), anhydrous DMF (6 mL), and 2.2 eq. of $POCl_3$ (0.6 mL, 6.6 mmol); 100 °C, 4 h, ice water (5 mL), sat. aq. solution of sodium hydrogen carbonate (10 mL), CH_2Cl_2 (3 × 10 mL); column chromatography (pentane-CH_2Cl_2 1 : 1).

Starting material: 2-chlorothiophene (**11**); product: 5-chlorothiophene-2-carbaldehyde (**14**). The product was isolated as a colorless liquid; yield: 35 mg (8 %).

Starting material: 2-bromothiophene (**12**); product: 5-chlorothiophene-2-carbaldehyde (**14**). The product was isolated as a colorless liquid; yield: 37 mg (8 %).

Starting material: 2-iodothiophene (**13**); products: mixture of 5-chloro-thiophene-2-carbaldehyde (**14**) / 5-iodothiophene-2-carbaldehyde (**16**) 1 : 0.33. The products were isolated as a colorless liquid; yield (both products): 99 mg (20 %).

*5-Chlorothiophene-2-carbaldehyde (**14**):* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, J = 4.0 Hz, 1 H, H_{arom}), 7.57 (d, J = 4.0 Hz, 1 H, H_{arom}), 9.78 (s, 1 H, C*H*O). The NMR data were in accordance with the literature [10].

*5-Iodothiophene-2-carbaldehyde (**16**):* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 2 H, H_{arom}), 9.77 (s, 1 H, C*H*O). The NMR data were in accordance with the literature [14].

*4-(Thien-3-yl)morpholine (**20**)*

4-(Thien-3-yl)morpholine (**20**) was synthesized according to the literature [15] from 3-bromothiophene. The product was isolated as a colorless solid; yield: 499 mg (80 %), m. p. 90 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.07 – 3.10 (m, 4 H, CH_2NCH_2), 3.83 – 3.85 (m, 4 H, CH_2OCH_2), 6.20 (dd, J = 3.0, 1.6 Hz, 1 H, *H*-2$_{arom}$), 6.86 (dd, J = 5.2, 1.6 Hz, 1 H, *H*-4$_{arom}$), 7.25 (dd, J = 5.2, 3.0 Hz, 1 H, *H*-5$_{arom}$). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.7 (2 C, *C*H_2NCH_2), 66.6 (2 C, *C*H_2OCH_2), 100.4 (1 C, *C*-2$_{arom}$), 119.6 (1 C, *C*-4$_{arom}$), 125.5 (2 C, *C*-5$_{arom}$), 152.4 (2 C, *C*-3$_{arom}$). – MS (EI, 70 eV): m/z (%) = 169 (54) $[M]^+$, 149 (21), 125 (13), 111 (100), 97 (32). The NMR data were in accordance with the literature [15].

*3-(4-Morpholino)thiophene-2-carbaldehyde (**21**)*

Method I: The product was synthesized according to the general procedure from 4-(thienyl-3-yl)morpholine (**20**) (75 mg, 0.444 mmol), anhydrous DMF (0.6 mL), and 1.1 eq. of $POCl_3$ (0.037 mL, 0.488 mmol); 50 °C; 1.5 h, ice water (5 mL), sat. aq. solution of sodium hydrogen carbonate (10 mL), CH_2Cl_2 (3 × 10 mL); column chromatography (petroleum ether-ethyl acetate 1 : 1). The product was isolated as a yellow solid; yield: 54 mg (62 %), m. p. 55 °C.

Method II: The product was synthesized according to the general procedure from 4-(2-bromo-3-thienyl)morpholine (**23**) (20 mg, 0.081 mmol), anhydrous DMF (0.12 mL), and 1.1 eq. of $POCl_3$ (0.008 mL, 0.089 mmol); 50 °C, 4.5 h, ice water (5 mL), sat. aq. solution of sodium hydrogen carbonate (5 mL), CH_2Cl_2 (3 × 5 mL); column chromatography (petroleum ether-ethyl acetate 2 : 1). The product was isolated as a yellow solid; yield: 4 mg (25 %), m. p. 55 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.33 – 3.36 (m, 4 H,

CH_2NCH_2), 3.85 – 3.87 (m, 4 H, CH_2OCH_2), 6.82 (d, J = 5.3 Hz, 1 H, H_{arom}), 7.62 (dd, J = 5.3, 0.8 Hz, 1 H, H_{arom}), 9.87 (d, J = 0.8 Hz, 1 H, C*H*O). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.1 (2 C, CH_2NCH_2), 66.7 (2 C, CH_2OCH_2), 120.9 (1 C, *C*-4_{arom}), 123.5 (1 C, *C*-2_{arom}), 135.7 (1 C, *C*-5_{arom}), 157.8 (1 C, *C*-3_{arom}), 180.8 (1 C, *C*HO). – IR (KBr): ν = 3114, 2965, 2917, 2892, 2862, 2833, 1641, 1529, 1448, 1428, 1370. 1358, 1310, 1255, 1191, 1168, 1110, 1066, 1028, 999, 923, 884, 853, 845, 819, 756, 703 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 197 (63) $[M]^+$, 180 (31), 166 (100), 149 (13), 140 (49), 125 (16), 111 (83), 105 (19), 97 (19), 91 (18). – HRMS ((+)-ESI): m/z = 198.0589 (calcd. 198.0589 for $C_9H_{12}NO_2S$, $[M+H]^+$).

*4-(2-Chloro-3-thienyl)morpholine (**22**)*

Under an atmosphere of nitrogen and at 0 °C *N*-chlorosuccinimide (124 mg, 0.931 mmol) was added in small portions to a solution of 4-(thien-3-yl)morpholine (**20**) (150 mg, 0.887 mmol) in anhydrous DMF (7 mL). The reaction mixture was stirred for 1 h at 0 °C in the dark and then brine (10 mL) was added. The aq. fraction was extracted with ethyl acetate (3 × 15 mL), and the organic fraction was washed with water and dried (magnesium sulfate). After evaporation of the solvent the product was purified by column chromatography (petroleum ether-ethyl acetate 4 : 1). The product was isolated as a light-brown oil; yield: 175 mg (97 %). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.06 – 3.08 (m, 4 H, CH_2NCH_2), 3.83 – 3.85 (m, 4 H, CH_2OCH_2), 6.79 (d, J = 5.9 Hz, 1 H, *H*-4_{arom}), 7.04 (d, J = 5.9 Hz, 1 H, *H*-5_{arom}). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.5 (2 C, CH_2NCH_2), 67.1 (2 C, CH_2OCH_2), 114.0 (1 C, *C*Cl), 120.1 (1 C, *C*-4_{arom}), 121.6 (1 C, *C*-5_{arom}), 146.9 (1 C, *C*-3_{arom}). – MS (EI, 70 eV): m/z (%) = 203 (67) $[M]^+$, 145 (100).

*4-(2-Bromo-3-thienyl)morpholine (**23**)*

Under an atmosphere of nitrogen and at 0 °C *N*-bromosuccinimide (22 mg, 0.124 mmol) was added in small portions to a solution of 4-(thien-3-yl)morpholine (**20**) (20 mg, 0.118 mmol) in anhydrous DMF (0.9 mL). The reaction mixture was stirred for 1 h at 0 °C in the dark, and then brine (10 mL) was added. The aq. fraction was extracted with ethyl acetate (3 × 15 mL), and the organic fraction was washed with water and dried (magnesium sulfate). After evaporation of the solvent the product was purified by column chromatography (petroleum ether-ethyl acetate 4 : 1) and isolated as a colorless oil; yield: 22 mg (75 %). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.04 – 3.07 (m, 4 H, CH_2NCH_2), 3.84 – 3.86 (m, 4 H, CH_2OCH_2), 6.80 (d, J = 5.8 Hz, 1 H, *H*-4_{arom}), 7.22 (d, J = 5.8 Hz, 1 H, *H*-5_{arom}). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.9 (2 C, CH_2NCH_2), 67.1 (2 C, CH_2OCH_2), 99.0 (1 C, *C*Br), 120.5 (1 C, *C*-4_{arom}), 125.0 (1 C, *C*-5_{arom}), 149.4 (1 C, *C*-3_{arom}). – MS (EI, 70 eV): m/z (%) = 247 (53) $[M]^+$, 189 (100), 149 (20), 123 (17), 111 (29), 97 (41).

*4-(2,5-Dichloro-3-thienyl)morpholine (**24**)*

This compound was synthesized as described above for **20** [15] from 3-bromo-2,5-dichlorothiophene (1.000 g, 4.351 mmol) as starting material and with a reaction time of 1.5 d. The product was purified by column chromatography (petroleum ether-ethyl acetate 6 : 1) and isolated as a light-brown solid; yield: 74 mg (7 %), m. p. 65 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.01 – 3.04 (m, 4 H, CH_2NCH_2), 3.81 – 3.83 (m, 4 H, CH_2OCH_2), 6.67 (s, 1 H, *H*-4_{arom}). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.4 (2 C, CH_2NCH_2), 66.9 (2 C, CH_2OCH_2), 110.9 (1 C, *C*-2_{arom}), 119.9 (1 C, *C*-4_{arom}), 125.4 (1 C, *C*-5_{arom}), 146.0 (1 C, C-3_{arom}). – IR (KBr): ν = 2961, 2910, 2892, 2855, 2827, 1554, 1450, 1380, 1353, 1332, 1305, 1281, 1264, 1199, 1170, 1118, 1085, 1069, 1037, 1009, 987, 922, 866, 811, 703 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 237 (48) $[M]^+$, 202 (10), 179 (100), 105 (14).

*5-Chloro-3-(4-morpholino)thiophene-2-carbaldehyde (**25**)*

The product was synthesized according to the general procedure from 4-(2,5-dichloro-3-thienyl)morpholine (**24**) (50 mg, 0.211 mmol), anhydrous DMF (0.4 mL), and 1.1 eq. of $POCl_3$ (0.021 mL, 0.232 mmol); 50 °C, 1 h, ice water (5 mL), sat. aq. solution of sodium hydrogen carbonate (10 mL), CH_2Cl_2 (3 × 10 mL); column chromatography (petroleum ether-ethyl acetate 4 : 1). The product was isolated as a light-yellow solid; yield: 16 mg (33 %), m. p. 132 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.33 – 3.36 (m, 4 H, CH_2NCH_2), 3.83 – 3.86 (m, 4 H, CH_2OCH_2), 6.69 (s, 1 H, *H*-4_{arom}), 9.76 (s, 1 H, C*H*O). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8 (2 C, CH_2NCH_2), 66.5 (2 C, CH_2OCH_2), 120.7 (1 C, *C*-4_{arom}), 122.0 (1 C, *C*-2_{arom}), 142.3 (1 C, *C*-5_{arom}), 156.3 (1 C, *C*-3_{arom}), 179.4 (1 C, *C*HO). – IR (KBr): ν = 3103, 2968, 2926, 2904, 2859, 1595, 1552, 1482, 1445, 1426, 1374, 1356, 1329, 1308, 1284, 1256, 1208, 1161, 1117, 1091, 1066, 1027, 994, 874, 836, 702 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 231 (75) $[M]^+$, 214 (50), 200 (88), 188 (73), 174 (69), 145 (72), 120 (57), 110 (100), 105 (650), 91 (26).

*2-(3,4-Ethylenedioxythiophene)carbaldehyde (**27**)*

The product was synthesized according to the general procedure from 3,4-ethylenedioxythiophene (**26**) (150 mg, 1.06 mmol), anhydrous DMF (1.5 mL), and 1.1 eq. of $POCl_3$ (0.11 mL, 1.16 mmol), 50 °C, 1.5 h; ice water (15 mL), sat. aq. solution of sodium hydrogen carbonate (15 mL), CH_2Cl_2 (3 × 15 mL); column chromatography (petroleum ether-ethyl acetate 2 : 1). The product was isolated as a colorless solid; yield: 148 mg (83 %), m. p. 141 °C. – ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.26 – 4.27 (m, 2 H, OCH_2CH_2O), 4.35 – 4.37 (m, 2 H, OCH_2CH_2O), 6.79 (d, J = 1.2 Hz, 1 H,

H-5$_{arom}$), 9.90 (d, J = 1.2 Hz, 1 H, C*H*O). – ^{13}C NMR (150 MHz, $CDCl_3$): δ = 64.3 (1 C, O*C*H$_2$CH$_2$O), 65.3 (1 C, OCH$_2$*C*H$_2$O), 110.7 (1 C, *C*-5$_{arom}$), 118.5 (1 C4, *C*-2$_{arom}$), 141.8 (1 C, *C*-3$_{arom}$), 148.4 (1 C, *C*-4$_{arom}$), 180.1 (1 C, *C*HO). The NMR data were in accordance with the literature [17].

*2,5-Dibromo-3,4-ethylenedioxythiophene (**28**)*

The synthesis according to the literature [18] afforded **28** as a colorless solid; yield: 939 mg (89 %), m. p. 98 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (s, 4 H, OC*H*$_2$C*H*$_2$O). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.9 (2 C, OC*H*$_2$*C*H$_2$O), 85.5 (2 C, *C*Br), 139.7 (2 C, OC$_{arom}$). – IR (KBr): ν = 2952, 2922, 2878, 1598, 1513, 1454, 1415, 1362, 1164, 1087, 1039, 977, 931, 903, 839, 749 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 300 (100) [M]$^+$, 273 (24), 188 (35), 163 (20), 147 (23), 123 (78), 105 (92), 95 (72), 91 (41).

*2-Bromo-3,4-ethylenedioxythiophene (**29**)*

This compound was synthesized in a process similar to the literature protocol [19]. Under an atmosphere of nitrogen *N*-bromosuccinimide (376 mg, 2.11 mmol) was added in small portions to a solution of 3,4-ethylenedioxythiophene (**26**) (300 mg, 2.11 mmol) in anhydrous DMF (3.5 mL). The reaction mixture was stirred for 1 h at r. t. in the dark, and was then poured into ice water and extracted with diethyl ether (3 × 30 mL). The organic fraction was washed with brine and dried (magnesium sulfate). After evaporation of the solvent the product was purified by column chromatography (pentane-THF 20 : 1). The product was isolated as a colorless oil; yield: 243 mg (52 %). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18 – 4.21 (m, 2 H, OC*H*$_2$C*H*$_2$O), 4.25 – 4.28 (m, 2 H, OC*H*$_2$C*H*$_2$O), 6.34 (s, 1 H, *H*-5$_{arom}$). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.5 (1 C, OCH$_2$CH$_2$O), 65.0 (1 C, OCH$_2$CH$_2$O), 87.0 (1 C, *C*Br), 99.6 (1 C, *C*-5$_{arom}$), 140.0 (1 C, *C*-3$_{arom}$ or *C*-4$_{arom}$), 141.1 (1 C, *C*-3$_{arom}$ or *C*−4$_{arom}$). – IR (KBr): ν = 3112, 2984, 2927, 2874, 1497, 1450, 1418, 1363, 1269, 1246, 1183, 1154, 1070, 1036, 926, 899, 712 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 220 (100) [M]$^+$, 194 (13), 141 (28), 120 (31), 105 (73), 97 (27), 91 (28).

*5-Bromo-3,4-ethylenedioxythiophene-2-carbaldehyde (**30**) / 5-chloro-3,4-ethylenedioxythiophene-2-carbaldehyde (**31**)*

Method I: The products were synthesized according to the general procedure from 2-bromo-3,4-ethylenedioxythiophene (**29**) (100 mg, 0.452 mmol), anhydrous DMF (0.7 mL), and 1.1 eq. of $POCl_3$ (0.045 mL, 0.497 mmol); 50 °C, 3 h, ice water (15 mL), sat. aq. solution of sodium hydrogen carbonate (15 mL), CH_2Cl_2 (3 × 15 mL); column chromatography (petroleum ether-ethyl acetate 2 : 1). The products were isolated as colorless solids, a 1.00 : 0.22 mixture of **30** and **31**; yield (both products): 91 mg (84 %).

Method II: The products were synthesized according to the general procedure from 2,5-dibromo-3,4-ethylenedioxythiophene (**28**) (100 mg, 0.333 mmol), anhydrous DMF (0.5 mL), and 1.1 eq. of $POCl_3$ (0.033 mL, 0.366 mmol); 50 °C, 1 d, ice water (15 mL), sat. aq. solution of sodium hydrogen carbonate (15 mL), CH_2Cl_2 (3 × 15 mL); column chromatography (petroleum ether-ethyl acetate 2 : 1). The products were isolated as colorless solids, a 0.32 : 1.00 mixture of **30** and **31**; yield (both products): 47 mg (66 %).

*5-Bromo-3,4-ethylenedioxythiophene-2-carbaldehyde (**30**):* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.34 – 4.39 (m, 4 H, OC*H*$_2$C*H*$_2$O), 9.85 (s, 1 H, C*H*O).

*5-Chloro-3,4-ethylenedioxythiophene-2-carbaldehyde (**31**):* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.34 – 4.39 (m, 4 H, OC*H*$_2$C*H*$_2$O), 9.82 (s, 1 H, C*H*O).

[1] a) V. A. Zapol'skii, J. C. Namyslo, M. Gjikaj, D. E. Kaufmann, *Z. Naturforsch.* **2010**, *65b*, 843 – 860; b) V. A. Zapol'skii, R. Fischer, J. C. Namyslo, D. E. Kaufmann, *Bioorg. Med. Chem.* **2009**, *17*, 4206 – 4215; c) E. Nutz, V. A. Zapol'skii, D. E. Kaufmann, *Synthesis* **2009**, *16*, 2719 – 2724; d) V. A. Zapol'skii, J. C. Namyslo, A. E. W. Adam, D. E. Kaufmann, *Heterocycles* **2004**, *63*, 1281 – 1298.

[2] I. F. Perepichka, D. F. Perepichka (Eds.) *Handbook of Thiophene-based Materials*, Vol. 1+2, John Wiley, Chichester, **2009**.

[3] a) A. Vilsmeier, A. Haack, *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 119 – 122; b) G. Jones, S. P. Stanforthe, *Org. React.*, Vol. 49, John Wiley, New York, **1997**, pp. 1 – 330; c) O. G. Altinbas, D. E. Kaufmann, T. Clark, *J. Mol. Model.* **2011**, *12*, 3209 – 3217.

[4] S. A. Koz'min, N. A. Bumagin, I. P. Beletskaya, *Izvest. Akad. Nauk, Ser. Khim.* **1993**, *3*, 615.

[5] H. M. Chawla, N. Pant, B. Srivastava, *Tetrahedron Lett.* **2005**, *46*, 7259 – 7262.

[6] R. V. Kaberdin, V. I. Potkin, V. A. Zapol'skii, *Russ. Chem. Rev.* **1997**, *66*, 827 – 842.

[7] DFT calculations on the mechanism are in progress.

[8] R. G. Pews, J. E. Hunter, R. M. Wehmeyer, *Tetrahedron* **1993**, *49*, 4809 – 4820.

[9] C. A. Kuttruff, H. Zipse, D. Trauner, *Angew. Chem.* **2011**, *123*, 1438 – 1441; *Angew. Chem. Int. Ed.* **2011**, *50*, 1402 – 1405.

[10] B. Liégault, I. Petrov, S. I. Gorelsky, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 1047 – 1060.

[11] E. Campaigne, W. L. Archer, *J. Am. Chem. Soc.* **1953**, *75*, 989 – 991.

[12] P. Rajender Kumar, S. Raju, P. Satish Goud, M. Sailaja, M. R. Sarma, G. Om Reddy, M. Prem Kumar, V. V. R. M. Krishna Reddy, T. Suresha, P. Hegde, *Bioorg. Med. Chem.* **2004**, *12*, 1221 – 1230.
[13] Y. Liu, N. Xiang, X. Feng, P. Shen, W. Zhou, C. Weng, B. Zhao, S. Tan, *Chem. Commun.* **2009**, 2499 – 2501.
[14] M. D'Auria, D. Tofani, *Tetrahedron* **1992**, *48*, 9315 – 9322.
[15] M. D. Charles, P. Schultz, S. L. Buchwald, *Org. Lett.* **2005**, *7*, 3965 – 3968.
[16] S. Kirchmeyer, K. Reuter, *J. Mater. Chem.* **2005**, *15*, 2077 – 2088.
[17] M. Jessing, M. Brandt, K. J. Jensen, J. B. Christensen, U. Boas, *J. Org. Chem.* **2006**, *71*, 6734 – 6741.
[18] R. G. Hicks, M. B. Nodwell, *J. Am. Chem. Soc.* **2000**, *122*, 6746 – 6753.
[19] M. Belletête, S. Beaupré, J. Bouchard, P. Blondin, M. Leclerc, G. Durocher, *J. Phys. Chem. B* **2000**, *104*, 9118 – 9125.