Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1667–1674

Heteroarenium salts in synthesis. Highly functionalized tetra- and pentasubstituted pyridines

Andreas Schmidt,[a,*] Thorsten Mordhorst[a] and Martin Nieger[b]

[a]*Clausthal University of Technology, Institute of Organic Chemistry, Leibnizstrasse 6, D-38678 Clausthal-Zellerfeld, Germany*
[b]*Rheinische Friedrich-Wilhelms-Universität Bonn, Institute of Inorganic Chemistry, Gerhard-Domagk-Strasse 1, D-53121 Bonn, Germany*

Received 4 November 2005; revised 24 November 2005; accepted 28 November 2005

Available online 20 December 2005

Abstract—Activation of chloropyridines by heteroarenium substituents allows sequential substitutions by O-, N-, and S-nucleophiles. Reaction of 2,3,5,6-tetrachloropyridine and 4-ethylsulfanyl-2,3,5,6-tetrachloropyridine with 4-(dimethylamino)pyridine, 4-(pyrrolidin-1-yl)pyridine, or 4-aminopyridine results in the formation of 2,6-bis-heteroarenium substituted 3,5-dichloropyridines. On nucleophilic displacement of the heteroarenium substituents by O-, N-, or S-nucleophiles highly functionalized 3,5-dichloropyridines form which possess N^2,S^4,N^6-, O^2,S^4,O^6-, O^2,O^6-, N^2,N^6-, and S^2,S^6-substitution patterns.

1. Introduction

Substitution reactions on halogenated heteroaromatics are widely applied reactions in organic synthesis. An impressive number of monographs and review articles reflect that synthetically, biologically, pharmaceutically, or industrially important pyridines can be synthesized from halogenated precursors.[1–4] Heteroaromatic substitutions proceed by different mechanisms. Mostly, a two-step AE-mechanism[1–3] is observed, but S_N(ANRORC)-,[5] EA-,[6] or S_{RN1}-mechanisms[7] have also been described. It is also known that the 2-, 3-, and 4-positions of the pyridine ring system display different reactivities.[1–3] The 3-position is often inert against nucleophilic attacks,[8] unless EA-mechanisms by amide ions[9] or metal-catalyses are applied.[10]

However, the vast majority of known substitutions was limited to the synthesis of mono- or bisubstituted pyridines. Thus, the reaction of pentachloropyridine with aliphatic amines generates only mono-amino tetrachloropyridines.[11] Vigorous reaction conditions are necessary to form 3,4-bisamino substituted trichloropyridines[12] or lead to mixtures of compounds. These limitations cannot be circumvented by alternative pyridine syntheses such as Hantźsch synthesis,[13] Kröhnke synthesis,[14] gasphase reactions of aldehydes and ketones with acrolein and ammonia,[15] electrocyclic ring closures,[16] ring transformations,[17] cycloadditions,[18] directed metallations,[19] or transition-metal catalysed reactions.[20] As a consequence, the number of reported tetra- and penta-substituted pyridines is very small. The need for these pyridines, however, is reflected in recent publications dealing with sequential controlled substitution reactions on pentafluoropyridines as promising avenues for the synthesis of macrocycles.[21]

As part of an ongoing project we recently described the synthesis and characterization of mono-, tris-, and pentakis-heteroarenium substituted pyridines bearing up to 10 positive charges within a common π-electron system.[22] These heteroarenium salts proved to be valuable starting materials for the regioselective synthesis of hitherto unavailable pyridine ethers[23] and pyridine thioethers.[24] We report here the scope and limitations of reactions leading to first examples of N^2,S^4,N^6-trisubstituted dichloropyridines, and to a variety of O^2,S^4,O^6-trisubstituted as well as O^2,O^6-, N^2,N^6-, and S^2,S^6-disubstituted dichloropyridines, which are symmetrically ($R^2=R^3$, Fig. 1) or non-symmetrically substituted ($R^2\neq R^3$).

2. Results and discussion

2.1. Activation of pentachloropyridine by heteroarenium substituents

Our earlier work reveals that the 4-chlorine atom of pentachloropyridine is the most susceptible leaving group toward substitution reactions with nucleophilic

Keywords: Heteroarenium; Pyridines; Nucleophiles.
* Corresponding author. Tel.: +49 5323 723861; fax: +49 5323 722858; e-mail: schmidt@ioc.tu-clausthal.de

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.065

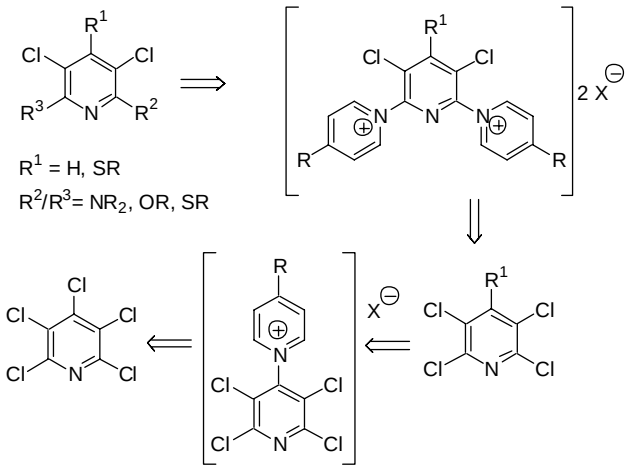
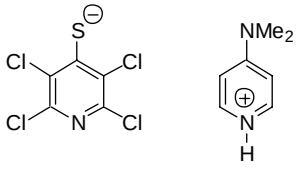


Figure 1. Retrosynthesis of substituted pyridines, available by sequential regioselective substitutions on heteroarenium activated chlorinated pyridines.

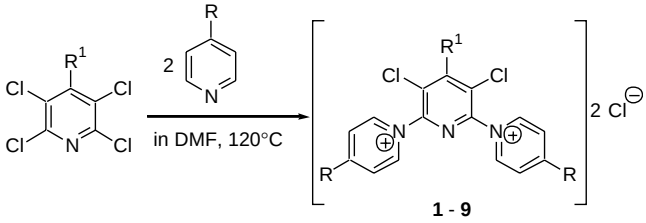
heteroaromatics such as 4-(dimethylamino)pyridine (DMAP), 4-(pyrrolidino)pyridine, and 1-methylimidazole.[22] We therefore focussed our interest on substitution reactions on pyridines without chlorine in the 4-position. In view of the interest in 4-sulfanyl-substituted pyridines (most of which are patented[25]) and other pyridine thioethers as bacterizides,[26] pesticides,[27] and intermediates for the synthesis of fungicides[28] and other biologically active compounds,[29] we focussed our interest on tetrachloro-4-sulfanylpyridines as starting materials. No substitution, however, was observable starting from 2,3,5,6-tetrachloropyridine-4-thiol or tetrachloropyridines with oxygen-or amino-groups in the 4-position under the reaction conditions applied. Deprotonation of acidic groups such as the SH-group resulted in a considerably decreased leaving group tendency of the α-chlorine substituents. Thus, treatment of 2,3,5,6-tetrachloro-pyridine-4-thiol with DMAP gave the salt 4-(dimethylamino)pyridinium 2,3,5,6-tetrachloropyridine-4-thiolate in quantitative yield (Scheme 1).



Scheme 1.

We found that 4-ethylsulfanyl-2,3,5,6-tetrachloropyridine, prepared regioselectively in 93% yield starting from 4-dimethylamino-(2,3,5,6-tetrachloropyridin-4-yl)pyridinium chloride,[24] does react with 4-aminopyridine, 4-(dimethylamino)pyridine, and 4-(pyrrolidino)pyridine to the bis-heteroarenium salts **1**, **4**, and **7**, respectively, (Table 1). Correspondingly, 4-(2-propylsulfanyl)-2,3,5,6-tetrachloro-pyridine gives **2**, **5**, and **8**. 2,3,5,6-Tetrachloro-pyridine affords the bis-heteroarenium salts **3**, **6**, and **9** in very good to excellent yields. All reactions were conducted at 120 °C in DMF, from which the salts precipitated in analytical purity on addition of ethyl acetate. The salts **1**–**9** are soluble in water, alcohols, amines, thiols, and DMF,

Table 1. Preparation of the bis-heteroarenium substituted pyridines



1 - 9

	R^1	R	Bis-hetero-arenium salt	Yield (%)
1	S–Et	$–NH_2$	**1**	54
2	S–*i*Pr	$–NH_2$	**2**	61
3	H	$–NH_2$	**3**	73
4	S–Et	$–N(CH_3)_2$	**4**	90
5	S–*i*Pr	$–N(CH_3)_2$	**5**	89
6	H	$–N(CH_3)_2$	**6**	95
7	S–Et	Pyrrolidin-1-yl	**7**	65
8	S–*i*Pr	Pyrrolidin-1-yl	**8**	66
9	H	Pyrrolidin-1-yl	**9**	99

stable on storage in air and on heating to 150 °C. The amino derivatives (**1**, **2**, **3**) are slightly hygroscopic.

Suitable single crystals of the bis-heteroarenium salt **5** as tetrafluoroborate were obtained by slow evaporation of a concentrated solution in H_2O:EtOH:HBF_4 (50% in H_2O)= 1:1:1. The molecular structure and the crystallographic numbering are shown in Figure 2. The dication **5** crystallized triclinic. The two pyridinium rings are twisted. Two different dihedral angles N1–C2–N21–C22 [123.4(3)°] and N1–C6–N61–C66 [115.3(3)°] were determined. The corresponding C2–N21 and C6–N61 bond distances (crystallographic numbering) are 144.2(3) pm, which corresponds to long C(sp^2)–N bonds. The dimethylamino group is joined to the pyridinium ring by a shortened C–N bond, the bond length of which was determined to be 133.2(4) and 133.2(4) pm. Bond distances of C22–C23 = 134.6(4) and C62–C63 = 134.9(4) pm do not hint at quinoidal characters of the pyridinium substituents.

2.2. Reaction of the bis-heteroarenium salts

Scope and limitations of substitution reactions of bis-heteroarenium salts to highly functionalized and hitherto unknown pyridines were investigated by examining first the reaction with O-, N-, and S-nucleophiles. 4-(Pyrrolidin-1-yl)pyridine gave the highest yields of the corresponding bis-heteroarenium salts **7**–**9**, but to our experience 4-(dimethylamino)pyridinium had the best leaving group tendencies for substitution reactions. Table 2 shows the reactions of the DMAP derivatives **4**, **5**, and **6** with oxygen nucleophiles. Sodium methanolate in methanol changed the heteroarenium substituents of **4** to methoxy groups to give **10**, which is a new substance (Table 2, entry 1). Likewise, the same reaction conditions converted **5** to **14** and **6** to **18** (entries 5 and 9, respectively). The synthesis of 3,5-dichloro-2,6-dimethoxypyridine **18** was described earlier. It was formed on reaction of 2,3,5,6-tetrachloropyridine with sodium methanolate in moderate yield.[30] No reaction occured on treatment of **4**, **5**, and **6** with 4-methoxyphenol in

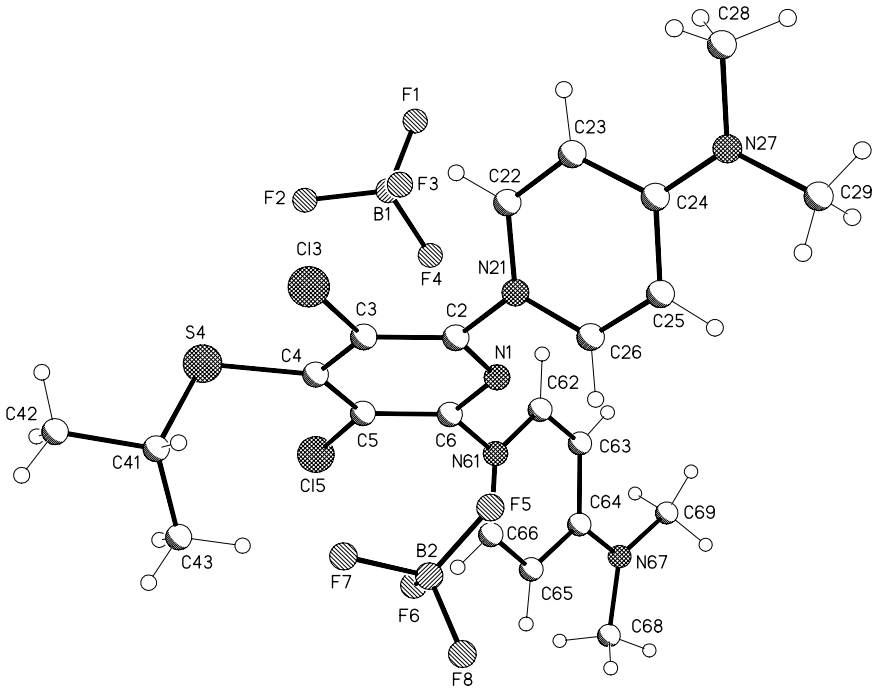
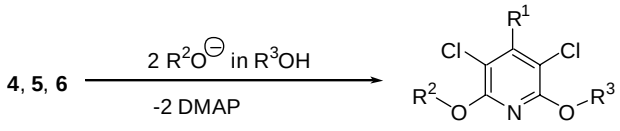


Figure 2. Molecular structure of **5**.

Table 2. Reaction of the dications **4**, **5**, and **6** with O-nucleophiles

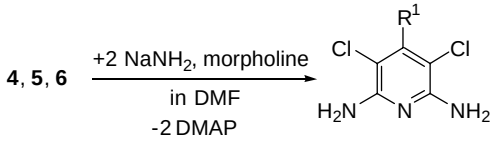


10 - 21

Entry	Starting material	R^1	R^2	R^3	Base added	Method	Product	Yield (%)
1	**4**	S–Et	Me	Me	Na	3 h/64 °C	**10**	57
2	**4**	S–Et	4-MeO-Ph	Me	$NaNH_2$	6 h/64 °C	**11**	23
3	**4**	S–Et	4-MeO-Ph	*i*Pr	$NaNH_2$	6 h/82 °C	**12**	20
4	**4**	S–Et	4-MeO-Ph	4-MeO-Ph	$NaNH_2$	6 h/82 °C	**13**	45
5	**5**	S–*i*Pr	Me	Me	Na	3 h/64 °C	**14**	59
6	**5**	S–*i*Pr	4-MeO-Ph	Me	$NaNH_2$	6 h/64 °C	**15**	43
7	**5**	S–*i*Pr	4-MeO-Ph	*i*Pr	$NaNH_2$	6 h/82 °C	**16**	15
8	**5**	S–*i*Pr	4-MeO-Ph	4-MeO-Ph	$NaNH_2$	6 h/82 °C	**17**	42
9	**6**	H	Me	Me	Na	3 h/64 °C	**18**	55
10	**6**	H	4-MeO-Ph	Me	$NaNH_2$	6 h/64 °C	**19**	40
11	**6**	H	4-MeO-Ph	*i*Pr	$NaNH_2$	6 h/82 °C	**20**	14
12	**6**	H	4-MeO-Ph	4-MeO-Ph	$NaNH_2$	6 h/82 °C	**21**	43

DMF in the presence of sodium amide. Non-symmetrically substituted pyridines ($R^1 \neq R^2 \neq R^3$), however, were obtained in a one-pot reaction of 4-methoxyphenol and $NaNH_2$ in methanol, although in moderate to low yields. Applying this reaction conditions pyridine thioethers with two different alkoxy groups in the α-positions of pyridine (**11**, **15**, **19**) were obtained. Thus, treatment of bis-heteroarenium salt **4** with 4-methoxyphenol in the presence of sodium amide in methanol gave 3,5-dichloro-4-ethylsulfanyl-2-(4-methoxyphenoxy)-6-methoxypyridine **11** (R^3=Me; entry 2). 2-Propanol as solvent resulted in the formation of a mixture of symmetrically and non-symmetrically substituted pyridines. The main products in the reactions of the bis-heteroarenium salts with 4-methoxyphenol in 2-propanol as solvent are the 2,6-(4-methoxyphenol)-substituted pyridines **13**, **17**, and **21** (Table 2, entries 4, 8 and 12), which can easily be separated from the non-symmetrically substituted α-(2-propoxy)pyridines **12**, **16**, and **20** (entries 3, 7 and 11) by column chromatography (silica gel; EtOAC/petrol ether=1:1), respectively. To the best of our knowledge, the compounds **10–17** are the first representatives of O^2,S^4,O^6-substituted 3,5-dichloropyridines. Even without chlorine in the β-positions this substitution pattern is very rare; we found that only five O^2,S^4,O^6-substituted pyridines have been synthesized by multi-step procedures[31] and patented[32] to date. O^2,O^6-substituted 3,5-dichloropyridines with hydrogen in the 4-position are pharmacologically interesting

Table 3. Reaction of the bis-heteroarenium salts **4**, **5**, and **6** with sodium amide



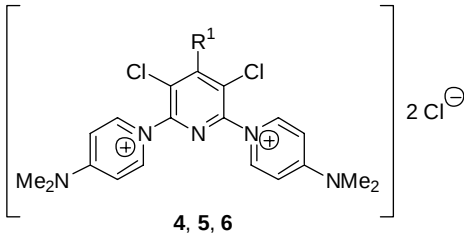
22 - 24

Entry	Starting material	R^1	Product	Yield (%)
1	**4**	S–Et	**22**	30
2	**5**	S–*i*Pr	**23**	55
3	**6**	H	**24**	20

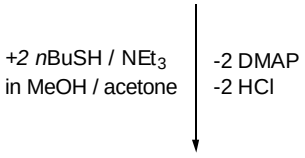
compounds; some derivatives with a broad variety of biological activities were prepared by multi-step procedures earlier.[33]

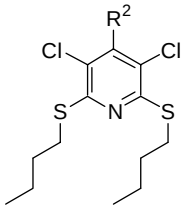
We next examined nitrogen nucleophiles. The dications **4** and **5** are attacked by amide in DMF in the presence of morpholine (or piperidine) to give the 2,6-diamino-4-sulfanylpyridines **22** and **23** (Table 3). Seemingly, these compounds are the first examples of N^2,S^4,N^6-substituted dichloropyridines. The bis-heteroarenium salt **6** affords 2,6-diamino-3,5-dichloropyridine **24** in low yield, which is also available starting from tetrachloroisonicotinic acid and ammonia at 200 °C in a sealed tube,[34] or from 2,6-diaminopyridine and hydrogen peroxide in hydrochloric acid in 60% yield.[35] No traces of the morpholine-substituted pyridines were isolable.

Table 4. Reaction of the dications with *n*-butylthiolate



4, 5, 6





25, 26

Entry	Starting material	R^1	R^2	Product	Yield (%)
1	**4**	S–Et	S–*n*Bu	**25**	46
2	**5**	S–*i*Pr	S–*n*Bu	**25**	40
3	**6**	H	H	**26**	25

Finally, we examined thiolates as reagents. In acetone, methanol, or mixtures of both and triethylamine as base substitutions were observed, and the pyridinium rings were replaced. Surprisingly, the ethylsulfanyl- and the 2-propylsulfanyl group at C-4 of **4** and **5** were substituted as well to yield **25**. The bis-heteroarenium salt **6** reacted in low yields to the bis-sulfanyl derivative **26** (Table 4).

In summary, we present an approach to highly functionalized pyridines possessing rare or hitherto unknown substitution patterns, which are of interest from chemical and biological viewpoints.

3. Experimental

3.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Digital FT-NMR Avance 400 and Avance DPX 200 spectrometers. Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, m = multiplet. ^{15}N NMR spectra: reference $MeNO_2$. FT-IR spectra were obtained on a Bruker Vektor 22 in the range of 400–4000 cm^{-1} (2.5% pellets in KBr). The electrospray ionisation mass spectra (ESIMS) were measured with an Agilent LCMSD Series HP1100 with APIES. Samples were sprayed from methanol at 0 V fragmentor voltage. Melting points are uncorrected. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 287940. 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). Some crystal data of **5**: $[C_{22}H_{27}Cl_2N_5S]^{2+}2\,[BF_4]^-$, M = 638.07; space group P-1 (No. 2); dimensions 0.40×0.20×0.10 mm, a = 9.2815(6), b = 9.5981(4), c = 15.9010(9) Å; α = 93.103(3)°, β = 90.874(3)°; γ = 94.325(3)°, V = 1410.16(13) $Å^3$, D_c = 1.503 Mg m^{-3}, Z = 2, μ(Mo Kα) = 0.380 mm^{-1}; T = 123(2) K; $F(000)$ = 652, 10104 reflections were collected in a Nonius KappaCD diffractometer ($2\Theta_{max}$ = 50°, $-11 \le h \le 10$, $-11 \le k \le 11$, $-16 \le l \le 18$), 4934 symmetry independent reflections (R_{int} = 0.0347) were used for the structure solution (direct methods)[36] and refinement (full-matrix least-squares on F^2,[37] 365 parameters), non-hydrogen atoms were refined anisotropically, H atoms localized by difference electron density, and were defined using a riding model; $wR2$ (all data) = 0.1182 [$R1$ = 0.0482 for 3741 $I > 2\sigma(I)$].

3.2. General procedure for the preparation of dications (1–9)

2,3,5,6-Tetrachloropyridine (2.17 g, 10 mmol) or 2,3,5,6-tetrachloro-4-ethylsulfanylpyridine[24] (2.77 g, 10 mmol) or 2,3,5,6-tetrachloro-4-(2-propylsulfanyl)pyridine (2.91 g, 10 mmol) and 4-aminopyridine (1.88 g, 20 mmol) or 4-dimethylaminopyridine (2.44 g, 20 mmol) or 4-(pyrrolidin-1-yl)pyridine (2.96 g, 20 mmol) were dissolved in 200 mL of DMF and stirred for 3 h at 120 °C. After cooling to room temperature 200 mL of ethyl acetate were added whereupon yellow precipitates formed, which were filtered off, washed with ethyl acetate, and dried in vacuo.

3.2.1. 1,1′-Bis[4-amino-(3,5-dichloro-4-ethylsulfanyl-pyridine-2,6-diyl)pyridinium]dichloride (1). Yellow solid, mp 317 °C (Found: C, 43.54; H, 4.56; N, 15.13. $C_{17}H_{17}Cl_4N_5S$ requires C, 43.89; H, 3.68; N, 15.05); δ_H [D_2O–CD_3OD (1/1)] 8.34 (d, ^3J=7.9 Hz, 4H), 7.05 (d, ^3J=7.9 Hz, 4H), 3.32 (q, 2H; ^3J=7.4 Hz, CH_2), 1.33 (d, ^3J=7.4 Hz, 3H; CH_3), no signals of the amino groups were detectable due to H/D exchange; δ_C [D_2O–CD_3OD (1/1)] 160.3, 153.5, 146.4, 141.7, 132.4, 109.2, 29.9, 14.3; ν_{max} (KBr) (cm^{-1}) 1655, 1543, 1376, 1202, 843.

3.2.2. 1,1′-Bis[4-amino-(3,5-dichloro-4-(2-propylsulfanyl)-pyridine-2,6-diyl)pyridinium]dichloride (2). Yellow solid, dec>260 °C (Found: C, 43.74; H, 4.73; N, 14.60. $C_{18}H_{19}Cl_4N_5S$ requires C, 45.11; H, 4.00; N, 14.61); δ_H [DMSO] 9.47 (s, 4H; NH_2), 8.58 (d, ^3J=7.3 Hz, 4H), 7.16 (d, ^3J=7.3 Hz, 4H), 3.94 (h, ^3J=6.6 Hz, 1H), 1.32 (d, ^3J=6.6 Hz, 6H); δ_C [DMSO] 160.1, 150.6, 146.3, 141.9, 132.7, 109.0, 41.2, 23.4; ν_{max} (KBr) (cm^{-1}) 3433, 3257, 3095, 1661, 1542, 1376, 1198, 1165, 1103, 846.

3.2.3. 1,1′-Bis[4-amino-(3,5-dichloro-pyridine-2,6-diyl)-pyridinium]dichloride (3). Yellow solid, mp 255 °C (Found: C, 43.72; H, 4.20; N, 17.20. $C_{15}H_{13}Cl_4N_5\cdot{}^1/_2\ H_2O$ requires C, 43.50; H, 3.41; N, 16.91); δ_H [DMSO–D_2O (1/1)] 8.97 (s, 1H), 8.53 (d, ^3J=7.6 Hz, 4H), 7.11 (d, ^3J=7.6 Hz, 4H), no signals of the amino groups detectable due to H/D exchange; δ_C [DMSO–D_2O (1/1)] 159.7, 145.8, 144.5, 141.8, 127.4, 108.9; ν_{max} (KBr) (cm^{-1}) 3059, 1663, 1542, 1387, 1285, 1189, 1105, 842.

3.2.4. 1,1′-Bis[4-dimethylamino-(3,5-dichloro-4-ethylsulfanyl-pyridine-2,6-diyl)pyridinium]dichloride (4). Yellow solid, mp 238 °C (Found: C, 45.38; H, 5.14; N, 13.46; S, 5.57. $C_{21}H_{25}Cl_4N_5S\cdot2H_2O$ requires C, 45.25; H, 5.24; N, 12.57; S, 5.75); δ_H [DMSO] 8.80 (d, ^3J=7.8 Hz, 4H), 7.32 (d, ^3J=7.8 Hz, 4H), 3.37 (q, ^3J=7.3 Hz, 2H), 3.36 (s, 12H), 1.32 (t, ^3J=7.3 Hz, 3H); δ_C [DMSO] 156.5, 151.2, 146.1, 141.1, 132.0, 107.6, 40.5, 29.8, 15.3; ν_{max} (KBr) (cm^{-1}) 1648, 1577, 1543, 1406, 1380, 1219, 829.

3.2.5. 1,1′-Bis[4-dimethylamino-(3,5-dichloro-4-(2-propylsulfanyl)-pyridine-2,6-diyl)pyridinium]dichloride (5). Yellow solid, mp 215 °C (Found: C, 49.34; H, 4.95; N, 12.69; $C_{22}H_{27}Cl_4N_5S$ requires: C, 49.36; H, 5.08; N, 13.08); δ_H [DMSO] 8.82 (d, ^3J=7.8 Hz, 4H), 7.33 (d, ^3J=7.8 Hz, 4H), 4.00 (h, ^3J=6.6 Hz, 1H), 3.36 (s, 12H), 1.37 (d, ^3J=6.6 Hz, 6H); δ_C [DMSO] 156.5, 150.5, 146.2, 141.1, 133.0, 107.6, 48.4, 40.4, 23.4; ν_{max} (KBr) (cm^{-1}) 3409, 1648, 1578, 1407, 1380, 1222, 1163.

3.2.6. 1,1′-Bis[4-dimethylamino-(3,5-dichloro-pyridine-2,6-diyl)pyridinium]dichloride (6). Yellow solid, mp 134 °C (Found: C, 43.45; H, 6.04; N, 14.07; $C_{19}H_{21}Cl_4N_5\cdot3{,}5H_2O$ requires C, 43.57; H, 5.38; N, 13.36); δ_H [DMSO] 9.20 (s, 1H), 8.75 (d, ^3J=7.8 Hz, 4H), 7.29 (d, ^3J=7.8 Hz, 4H), 3.34 (s, 12H); δ_C [DMSO] 156.5, 145.9, 144.4, 140.9, 127.5, 107.6, 40.5; ν_{max} (KBr) (cm^{-1}) 1649, 1582, 1562, 1429, 1406, 1230, 1212, 1105, 832.

3.2.7. 1,1′-Bis[4-pyrrolidino-(3,5-dichloro-4-(ethylsulfanyl)-pyridine-2,6-diyl)pyridinium]dichloride (7). Yellow solid, mp 204 °C (Found: C, 49.99; H, 5.66; N, 12.41; S, 5.02; $C_{25}H_{29}Cl_4N_5S\cdot2H_2O$ requires C, 49.27; H, 5.46; N, 11.49; S, 5.26); δ_H [DMSO–CD_3OD (1/1)] 8.68 (d, ^3J=7.7 Hz, 4H), 7.31 (d, ^3J=7.7 Hz, 4H), 4.51 (q, ^3J=6.9 Hz, 2H), 3.90–4.10 (m, 8H), 2.40–2.60 (m, 8H), 1.68 (t, ^3J=6.9 Hz, 3H); δ_C [DMSO–CD_3OD (1/1)] 154.2, 146.6, 145.0, 140.8, 129.9, 107.6, 49.2, 29.9, 24.6, 14.2; ν_{max} (KBr) (cm^{-1}) 1648, 1572, 1430, 1214, 1087, 828.

3.2.8. 1,1′-Bis[4-pyrrolidino-(3,5-dichloro-4-(2-propylsulfanyl)-pyridine-2,6-diyl)-pyridinium]dichloride (8). Yellow solid, mp 214 °C (Found: C, 47.22; H, 6.15; N, 11.38; S, 4.81; $C_{26}H_{31}Cl_4N_5S\cdot4H_2O$ requires C, 47.35; H, 5.96; N, 10.62; S, 4.81); δ_H [DMSO] 8.74 (d, ^3J=7.7 Hz, 4H), 7.13 (d, ^3J=7.7 Hz, 4H), 3.97 (h, ^3J=6.8 Hz, 1H), 3.65 (s, 8H), 2.03 (s, 8H), 1.34 (d, ^3J=6.8 Hz, 6H); δ_C [DMSO] 153.6, 150.5, 146.3, 141.0, 132.9, 108.3, 49.1, 41.3, 24.5, 23.4; ν_{max} (KBr) (cm^{-1}) 1647, 1571, 1548, 1429, 1215, 1087, 828.

3.2.9. 1,1′-Bis[4-pyrrolidino-(3,5-dichloro-pyridine-2,6-diyl)-pyridinium]dichloride (9). Pale yellow solid, mp 232 °C (Found: C, 48.95; H, 5.87; N, 12.82; $C_{23}H_{25}Cl_4N_5\cdot3H_2O$ requires C, 48.69; H, 5.51; N, 12.34); δ_H [DMSO] 9.22 (s, 1H), 8.76 (d, ^3J=7.7 Hz, 4H), 7.15 (d, ^3J=7.7 Hz, 4H), 3.68 (s, 8H), 2.06 (s, 8H); δ_C [DMSO] 153.6, 146.0, 144.4, 140.9, 127.5, 108.3, 49.1, 24.5; ν_{max} (KBr) (cm^{-1}) 1648, 1573, 1429, 1389, 1351, 1206, 1105, 831.

3.3. General procedure for the reaction of the 1,1′-bis[4-dimethylamino-(3,5-dichloro-pyridine-2,6-diyl)pyridinium]-dichlorides 4, 5, and 6 with sodium methanolate to 10, 14, and 18

In 100 mL of methanol were dissolved the salt **4** (5.21 g, 10 mmol), or **5** (5.35 g, 10 mmol), or **6** (4.61 g, 10 mmol) and sodium methanolate (2.70 g, 50 mmol), respectively. After 6 h stirring at reflux temperature the solvent was distilled off, and the residue was worked up by chromatography (silica gel 60 HF_{254} from Merck, ethyl acetate–petrol ether (1/1)).

3.3.1. 3,5-Dichloro-4-ethylsulfanyl-2,6-dimethoxypyridine (10). Colourless liquid; (Found: C, 40.04; H, 3.71; N, 5.14; S, 11.81; $C_9H_{11}Cl_2NO_2S$ requires C, 40.31; H, 4.18; N, 5.22; S, 11.96); δ_H [$CDCl_3$] 4.01 (s, 6H), 3.04 (q, ^3J=7.4 Hz, 2H), 1.23 (t, ^3J=7.4 Hz, 3H); δ_C [$CDCl_3$] 156.0, 145.8, 113.2, 54.6, 29.1, 14.8; ν_{max} (NaCl) (cm^{-1}) 2984, 2950, 2867, 1562, 1538, 1470, 1448, 1370, 1318, 1200, 1121, 1098, 1031, 787, 746; GC–MS: m/z=268 (M, 100); 237 (M−C_2H_5, 9); 199 (M−C_5H_5–Cl, 13) amu.

3.3.2. 3,5-Dichloro-2,6-dimethoxy-4-(2-propylsulfanyl)-pyridine (14). Colourless liquid; (Found: C, 42.58; H, 4.66; N, 4.96; S, 10.93; $C_{10}H_{13}Cl_2NO_2S$ requires C, 42.56; H, 4.64; N, 4.96; S, 11.36); δ_H [$CDCl_3$] 4.02 (s, 6H), 3.74 (h, ^3J=6.7 Hz, 1H), 1.27 (d, ^3J=6.7 Hz, 6H); δ_C [$CDCl_3$] 156.1, 145.9, 113.6, 54.6, 39.4, 23.1; ν_{max} (NaCl) (cm^{-1}) 2951, 2866, 1558, 1538, 1471, 1446, 1369, 1317, 1244, 1199, 1121, 1097, 786, 749; GC–MS: m/z=282 (M, 100); 238 (M−C_3H_7, 5) amu.

3.3.3. 3,5-Dichloro-2,6-dimethoxypyridine (18). White solid, mp 48 °C (Found: C, 40.41; H, 3.62; N, 6.67;

$C_7H_7Cl_2NO_2$ requires C, 40.41; H, 3.39; N, 6.73); δ_H [$CDCl_3$] 7.58 (s, 1H), 4.00 (s, 6H); δ_C [$CDCl_3$] 156.0, 139.9, 107.8, 54.4; ν_{max} (KBr) (cm^{-1}) 1582, 1470, 1398, 1225, 1095, 1009, 786, 739; GC–MS: m/z=208 (M, 100), 177 (M−CH_3O, 52) amu.

3.4. General procedure for the reaction of the 1,1′-bis[4-dimethylamino-(3,5-dichloropyridine-2,6-diyl)pyridinium]-dichlorides 4, 5, and 6 with 4-methoxyphenol in methanol to 11, 15, and 19

In 100 mL of methanol were dissolved the salt **4** (5.21 g, 10 mmol), or **5** (5.35 g, 10 mmol), or **6** (4.61 g, 10 mmol), and 4-methoxyphenol (2.48 g, 20 mmol), respectively. Then, sodium amide (0.78 g, 20 mmol) was added and the mixture was heated under reflux for 6 h. After this period the solvent was distilled off and the residue was worked up chromatographically (silica gel 60 HF_{254} from Merck, ethyl acetate–petrol ether (1/1)).

3.4.1. 3,5-Dichloro-4-ethylsulfanyl-2-(4-methoxyphenoxy)-6-methoxypyridine (11). Pale yellow liquid; (Found: C, 49.32; H, 4.29; N, 4.35; $C_{15}H_{15}Cl_2NO_3S$ requires C, 50.01; H, 4.20; N, 3.89); δ_H [$CDCl_3$] 7.07 (d, ^3J=9.2 Hz, 2H), 6.89 (d, ^3J=9.2 Hz, 2H), 3.82 (s, 3H), 3.67 (s, 3H), 3.09 (h, ^3J=7.4 Hz, 2H), 1.27 (t, ^3J=7.4 Hz, 3H); δ_C [$CDCl_3$] 157.2, 156.7, 156.0, 146.9, 145.8, 122.4 (overlapped), 114.1, 113.2, 55.5, 54.6, 29.1, 14.9; ν_{max} (NaCl) (cm^{-1}) 2951, 1561, 1504, 1460, 1369, 1247, 1198, 1101, 1033; GC–MS: m/z=361 (MH^+, 100) amu.

3.4.2. 3,5-Dichloro-2-(4-methoxyphenoxy)-6-methoxy-4-(2-propylsulfanyl)pyridine (15). Colourless liquid; (Found: C, 50.46; H, 4.24; N, 3.73; $C_{16}H_{17}Cl_2NO_3S$ requires C, 51.34; H, 4.58; N, 3.74); δ_H [$CDCl_3$] 7.01–7.11 (m, 2H), 6.82–6.92 (m, 2H), 3.78 (h, ^3J=6.7 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 1.29 (d, ^3J=6.7 Hz, 6H); δ_C [$CDCl_3$] 156.6, 155.9, 155.4, 146.8, 146.7, 122.3, 115.5, 114.0, 113.8, 55.3, 54.4, 39.5, 23.1; ν_{max} (NaCl) (cm^{-1}) 2951, 1558, 1505, 1462, 1367, 1246, 1196, 1097, 1034, 843; GC–MS: m/z=389 (M, 100) amu.

3.4.3. 3,5-Dichloro-2-(4-methoxyphenoxy)-6-methoxypyridine (19). Colourless liquid; (Found: C, 52.02; H, 3.69; N, 4.67; $C_{13}H_{11}Cl_2NO_3$ requires C, 50.57; H, 3.21; N, 4.75); δ_H [$CDCl_3$] 7.62 (s, 1H), 7.00–7.10 (m, 2H), 6.82–6.92 (m, 2H), 3.78 (s, 3H), 3.64 (s, 3H); δ_C [$CDCl_3$] 156.6, 155.8, 155.3, 146.8, 140.5, 122.3, 114.1, 109.9, 108.5, 55.4, 54.4; ν_{max} (NaCl) (cm^{-1}) 2954, 1578, 1506, 1469, 1409, 1380, 1222, 1192, 1095, 1036, 988, 837; GC–MS: m/z=329 (MH^+, 100), 264 (M−C_3H_7, 83), 108 (C_7H_7O, 53) amu.

3.5. General procedure for the reaction of the 1,1′-bis[4-dimethylamino-(3,5-dichloropyridine-2,6-diyl)pyridinium]-dichlorides 4, 5, and 6 with 4-methoxyphenol in 2-propanole to 12, 13, 16, 17, 20, and 21

In 100 mL of 2-propanol were dissolved the salt **4** (5.21 g, 10 mmol), or **5** (5.35 g, 10 mmol), or **6** (4.61 g, 10 mmol), and 4-methoxyphenol (2.48 g, 20 mmol), respectively. Then, sodium amide (0.78 g, 20 mmol) was dissolved and the mixture was heated at reflux temperature for 6 h. After this period the solvent was distilled off and the residue was chromatographed (silica gel 60, ethyl acetate–petrol ether (1/1)).

3.5.1. 3,5-Dichloro-4-ethylsulfanyl-2-(4-methoxyphenoxy)-6-(2-propoxy)-pyridine (12). Colourless liquid; (Found: C, 51.02; H, 4.71; N, 3.70; $C_{17}H_{19}Cl_2NO_3S$ requires C, 52.58; H, 4.93; N, 3.61); δ_H [$CDCl_3$] 7.05 (m, 2H), 6.89 (m, 2H), 4.70 (h, ^3J=6.2 Hz, 1H), 3.83 (s, 3H), 3.09 (h, ^3J=7.3 Hz, 2H), 1.28 (t, ^3J=7.3 Hz, 3H), 1.27 (d, ^{3}J=6.2 Hz, 6H); δ_C [$CDCl_3$] 160.4, 156.7, 155.2, 147.0, 146.4, 122.5, 122.4, 114.5, 114.1, 70.9, 55.6, 29.2, 21.6, 15.0; ν_{max} (NaCl) (cm^{-1}) 2979, 2931, 1557, 1504, 1374, 1246, 1195, 1095, 1036, 945; GC–MS: m/z=389 (MH^+, 100) amu.

3.5.2. 3,5-Dichloro-4-ethylsulfanyl-2,6-bis(4-methoxyphenoxy)-pyridine (13). Colourless solid, mp 82 °C; (Found: C, 55.41; H, 4.42; N, 3.10; S, 6.92; $C_{21}H_{19}Cl_2NO_4S$ requires C, 55.76; H, 4.23; N, 3.10; S, 7.09); δ_H [$CDCl_3$] 6.80–6.87 (m, 4H), 6.64–6.73 (m, 4H), 3.77 (s, 6H), 3.13 (q, ^3J=7.4 Hz, 2H), 1.31 (t, ^3J=7.4 Hz, 3H); δ_C [$CDCl_3$] 156.6, 155.3, 147.4, 146.5, 122.4, 115.2, 113.9, 55.4, 29.4, 15.0; ν_{max} (KBr) (cm^{-1}) 1559, 1501, 1369, 1249, 1193, 1029, 828; GC–MS: m/z=452 (M, 100) amu.

3.5.3. 3,5-Dichloro-2-(4-methoxyphenoxy)-6-(2-propoxy)-4-(2-propylsulfanyl)pyridine (16). Pale yellow liquid; (Found: C, 53.34; H, 5.64; N, 3.56; $C_{18}H_{21}Cl_2NO_3S$ requires C, 53.73; H, 5.26; N, 3.48); δ_H [$CDCl_3$] 7.00–7.10 (m, 2H), 6.85–6.95 (m, 2H), 4.70 (h, ^3J=6.3 Hz, 1H), 3.83 (s, 3H), 3.80 (h, ^3J=6.5 Hz, 1H), 1.31 (d, ^3J=6.3 Hz, 6H), 1.17 (d, ^3J=6.5 Hz, 6H); δ_C [$CDCl_3$] 156.7, 155.5, 155.3, 147.0, 146.5, 122.5, 115.9, 114.2, 113.4, 70.9, 55.6, 39.5, 23.3, 21.6; ν_{max} (NaCl) (cm^{-1}) 2977, 2931, 1558, 1503, 1374, 1246, 1196, 1109, 1037, 946, 832; GC–MS: m/z=403 (MH^+, 100), 359 (M−C_3H_7, 15), 317 (M−$2C_3H_7$, 28), 280 (M−$2C_3H_7$–Cl, 21) amu.

3.5.4. 3,5-Dichloro-2,6-bis(4-methoxyphenoxy)-4-(2-propylsulfanyl)pyridine (17). Pale yellow solid, mp 52 °C; (Found: C, 56.22; H, 4.78; N, 3.00; S, 6.80; $C_{22}H_{21}Cl_2NO_4S$ requires C, 56.66; H, 4.54; N, 3.00; S, 6.88); δ_H [$CDCl_3$] 6.86–6.90 (m, 2H), 6.62–6.72 (m, 2H), 3.84 (h, ^3J=6.6 Hz, 1H), 3.76 (s, 6H), 1.34 (d, ^3J=6.6 Hz, 6H); δ_C [$CDCl_3$] 156.6, 155.3, 147.5, 146.5, 122.5, 115.7, 113.9, 55.4, 39.7, 23.3; ν_{max} (KBr) (cm^{-1}) 2957, 2834, 1551, 1505, 1369, 1264, 1193, 1036, 825; GC–MS: m/z=467 (M, 100) amu.

3.5.5. 3,5-Dichloro-2-(4-methoxyphenoxy)-6-(2-propoxy)-pyridine (20). Colourless liquid; (Found: C, 54.41; H, 4.39; N, 4.35; $C_{15}H_{15}Cl_2NO_3$ requires C, 54.90; H, 4.61; N, 4.27); δ_H [$CDCl_3$] 7.66 (s, 1H), 7.00–7.08 (m, 2H), 6.85–6.93 (m, 2H), 4.71 (h, ^3J=6.3 Hz, 1H), 3.82 (s, 3H), 1.17 (d, ^3J=6.3 Hz, 6H); δ_C [$CDCl_3$] 156.7, 155.3, 155.2, 147.0, 140.5, 122.5, 114.1, 110.3, 107.7, 70.7, 55.6, 21.6; ν_{max} (NaCl) (cm^{-1}) 2980, 1569, 1505, 1436, 1247, 1218, 1191, 1092, 1036, 833; GC–MS: m/z=329 (MH^+, 100) amu.

3.5.6. 3,5-Dichloro-2,6-bis(4-methoxyphenoxy)pyridine (21). Colourless solid, mp 104 °C; (Found: C, 58.00; H, 3.49; N, 3.48; $C_{19}H_{15}Cl_2NO_4$ requires C, 58.18; H, 3.85; N, 3.57); δ_H [$CDCl_3$] 7.75 (s, 1H), 6.79–6.89 (m, 4H), 6.63–6.73 (m, 4H), 3.77 (s, 6H); δ_C [$CDCl_3$] 156.5, 155.2, 146.6, 141.1, 122.4, 113.9, 110.1, 55.5; ν_{max} (KBr) (cm^{-1}) 2958,

1574, 1508, 1428, 1249, 1221, 1180, 1091, 1034, 829; GC–MS: $m/z=392$ (M, 100) amu.

3.6. General procedure for the reaction of the 1,1′-bis[4-dimethylamino-(3,5-dichloropyridine-2,6-diyl)pyridinium]-dichlorides 4, 5, and 6 with sodium amide in DMF to 22–24

In 100 mL of DMF were dissolved the salt **4** (5.21 g, 10 mmol), or **5** (5.35 g, 10 mmol), or **6** (4.61 g, 10 mmol), and morpholine (8.2 g, 0.1 mol) as well as sodium amide (3.9 g, 0.1 mol), respectively. The mixture was stirred at 100 °C for 6 h. Then, the solvent was distilled off and the residue was chromatographed (silica gel 60, ethyl acetate–petrol ether (1/1)).

3.6.1. 2,6-Diamino-3,5-dichloro-4-ethylsulfanylpyridine (22). Yellow solid, mp 63 °C; (Found: C, 35.83; H, 4.11; N, 17.09; S, 13.62; $C_7H_9Cl_2N_3S$ requires C, 35.31; H, 3.81; N, 17.65; S, 13.46); δ_H [$CDCl_3$] 4.81 (s, 4H), 3.00 (q, $^3J=7.4$ Hz, 2H), 1.24 (t, $^3J=7.4$ Hz, 3H); δ_C [$CDCl_3$] 152.1, 142.5, 108.0, 29.2, 14.9; ν_{max} (KBr) (cm^{-1}) 3397, 3319, 1605, 1426, 1409, 1263, 746; GC–MS: $m/z=238$ (MH^+, 100) amu.

3.6.2. 2,6-Diamino-3,5-dichloro-4-(2-propylsulfanyl)-pyridine (23). Yellow solid, mp 64 °C; (Found: C, 38.49; H, 4.55; N, 15.98; S, 12.61; $C_8H_{11}Cl_2N_3S$ requires C, 38.10; H, 4.40; N, 16.66; S, 12.72); δ_H [$CDCl_3$] 4.89 (s, 4H), 3.65 (h, $^3J=6.6$ Hz, 1H), 1.27 (d, $^3J=6.6$ Hz, 6H); δ_C [$CDCl_3$] 152.1, 142.7, 108.3, 39.3, 23.2; ν_{max} (KBr) (cm^{-1}) 3425, 3323, 1627, 1603, 1531, 1412; GC–MS: $m/z=253$ (MH^+, 100); 208 ($M-C_3H_7$, 31); 175 ($M-C_3H_7S$, 43) amu.

3.6.3. 2,6-Diamino-3,5-dichloropyridine (24). Yellow solid, mp 202 °C; (Found: C, 33.87; H, 2.70; N, 24.00; $C_5H_5N_3Cl_2$ requires C, 33.73; H, 2.83; N, 23.60); δ_H [$CDCl_3$–CD_3OD (1/2)] 7.68 (s, 1H), the protons of the amino groups gave no signal due to H/D-exchange; δ_C [$CDCl_3$–CD_3OD (1/2)] 161.1, 140.0, 104.7; ν_{max} (KBr) (cm^{-1}) 3457, 3409, 3317, 1626, 1458, 1295, 902, 737; GC–MS: $m/z=180$ (MH^+, 100) amu.

3.7. General procedure for the reaction of the 1,1′-bis[4-dimethylamino-(3,5-dichloro-pyridine-2,6-diyl)pyridinium]-dichlorides 4, 5, and 6 to 2,4,6-tris(*n*-butylsulfanyl)-3,5-dichloropyridine (25)

In 100 mL of methanol were dissolved the salt **4** (5.21 g, 10 mmol) or **5** (5.35 g, 10 mmol), *n*-butylthiol (5.4 g, 50 mmol) and triethylamine (5.2 g, 50 mmol). The mixture was then stirred for 18 h at room temperature. Then, the solvent was distilled off and the residue was chromatographed (silica gel, ethyl acetate–petrol ether (1/1)).

3.7.1. 2,4,6-Tris(*n*-butylsulfanyl)-3,5-dichloropyridine (25). Colourless liquid; (Found: C, 49.79; H, 6.64; N, 3.05; S, 24.30; $C_{17}H_{27}Cl_2NS_3$ requires C, 49.50; H, 6.60; N, 3.40; S, 23.32); δ_H [$CDCl_3$] 3.17 (t, $^3J=7.5$ Hz, 4H), 2.97 (t, $^3J=7.1$ Hz, 2H), 1.72 (m, 4H), 1.66 (m, 2H), 1.46 (m, 4H), 1.43 (m, 2H), 0.95 (t, $^3J=7.5$ Hz, 6H), 0.89 (t, $^3J=7.1$ Hz, 3H); δ_C [$CDCl_3$] 155.4, 142.4, 127.7, 34.9, 31.8, 31.2, 30.7, 22.2, 21.7, 13.7, 13.5; ν_{max} (NaCl) (cm^{-1}) 2959, 2930, 2872, 1492, 1464, 1287, 1209, 1187, 1076, 806; GC–MS: $m/z=414$ (MH^+, 80); 376 (M−Cl, 100), 334 (M−Cl–C_3H_7, 38) amu.

3.7.2. Preparation of 2,6-bis(*n*-butylsulfanyl)-3,5-dichloro-pyridine (26). In 100 mL of methanol were dissolved 1,1′-bis[4-dimethylamino-(3,5-dichloropyridine-2,6-diyl)pyridinium]dichloride (5.21 g, 10 mmol), *n*-butylthiol (5.4 g, 50 mmol), and triethylamine (5.2 g, 50 mmol). The mixture was stirred for 18 h at room temperature. Then, the solvent was distilled off and the residue was chromatographed (silica gel 60, ethyl acetate–petrol ether (1/1)). Pale yellow liquid; (Found: C, 48.85; H, 6.22; N, 2.84; $C_{13}H_{19}Cl_2NS_2$ requires C, 48.14; H, 5.90; N, 4.32); δ_H [$CDCl_3$] 7.42 (s, 1H), 3.19 (t, $^3J=7.4$ Hz, 4H), 1.62–1.79 (m, 4H), 1.39–1.54 (m, 4H), 0.95 (t, $^3J=7.2$ Hz, 6H); δ_C [$CDCl_3$] 154.2, 135.2, 123.6, 38.8, 31.3, 22.2, 13.7; ν_{max} (NaCl) (cm^{-1}) 2957, 2930, 2873, 1545, 1515, 1464, 1371, 1334, 1218, 1147, 1062; GC–MS: $m/z=325$ (M, 100); 288 (M−Cl, 41), 266 (M−C_4H_9, 10) amu.

Acknowledgements

The Deutsche Forschungsgemeinschaft (DFG) is greatfully acknowledged for financial support. We thank Prof. F. Vögtle, Prof. K.-H. Dötz, and Prof. E. Niecke (University of Bonn) for providing the X-ray facilities.

References and notes

1. Spitzner, D. In Black, D. S. C., Ed.; Science of Synthesis; Thieme: Stuttgart, 2004; Vol. 15, pp 11–284.
2. Spitzner, D. In Kreher, E., Ed.; Houben-Weyl, Methoden der Organischen Chemie; Thieme: Stuttgart, 1994; Vol. E7b, pp 286–686.
3. *The Chemistry of Heterocyclic Compounds*, Weissberger A., Taylor, E. C., Eds.; Vol. 14: Pyridine and its Derivatives, Suppl. 1–4, Abramovitch, A., Ed., Wiley-Interscience: New York, 1974 and 1975.
4. Belen'kii, L. I.; Kruchkovskaya, N. D.; Gramenitskaya, V. N. *Adv. Heterocycl. Chem.* **1999**, *73*, 295.
5. de Bie, D. A.; Geurtsen, B.; Berg, I. E.; van der Plas, H. C. *J. Org. Chem.* **1986**, *51*, 3209.
6. (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Chemie: Weinheim, 1967. (b) Kauffmann, T.; Wirthwein, R. *Angew. Chem.* **1971**, *83*, 21. Angew. Chem., Int. Ed. Engl. **1971**, *10*, 20. (c) Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427.
7. (a) McGill, C. K.; Rappa, A. *Adv. Heterocycl. Chem.* **1988**, *44*, 1. (b) Boy, P.; Combellas, C.; Thiebault, A. *Synlett* **1991**, 923. (c) Beugelmans, R.; Chastanet, J. *Tetrahedron* **1993**, *49*, 7883.
8. (a) Jonckers, T. H. M.; Maes, B. U. W.; Lemiere, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027. (b) Connon, S.-J.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1245. (c) Kim, C.-S.; Russell, K. C. *J. Org. Chem.* **1998**, *23*, 8229. (d) Barlocco, D.; Cignarella, G.; Tondi, D.; Vianello, P.; Villa, S. *J. Med. Chem.* **1998**, *41*, 674.
9. Berry, D. J.; Wakefield, B. J. *J. Chem. Soc. C* **1969**, 2342.

10. (a) Gradel, B.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 568. (b) Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 5373. (c) Sakamoto, T.; Shiga, F.; Yasuhara, A.; Uchiyama, D.; Kondo, Y.; Yoshinori, Y. *Synthesis* **1992**, *8*, 746. (d) Ji, J.; Li, T.; Brunelle, W. H. *Org. Lett.* **2003**, *5*, 4611.
11. (a) Vorbrüggen, H. *Adv. Heterocycl. Chem.* **1990**, *49*, 117. (b) Collins, I.; Suschitzky, H. *J. Chem. Soc. C* **1970**, 1523. (c) Roberts, S. M.; Suschitzky, H. *Chem. Commun.* **1967**, 893.
12. (a) Bratt, J.; Iddon, B.; Mack, A. G.; Suschitzky, H.; Taylor, J. A.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 648. (b) Julia, L.; Rius, J.; Suschitzky, H. *Heterocycles* **1992**, *34*, 1539.
13. Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 269.
14. Kröhnke, F. *Synthesis* **1976**, 1.
15. Beschke, H. *Aldrichim. Acta* **1981**, *14*, 13.
16. Jutz, J. C. *Top. Curr. Chem.* **1978**, *73*, 125.
17. Katritzky, A. R. *Tetrahedron* **1980**, *36*, 679.
18. Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.
19. (a) Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187. (b) Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436. (c) Comins, D. L.; La Munyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773.
20. Undheim, K.; Benneche, T. *Adv. Heterocycl. Chem.* **1995**, *62*, 305.
21. (a) Sandford, G. *Eur. J. Org. Chem.* **2003**, *9*, 1465. (b) Chambers, R. D.; Hoskin, P. R.; Sandford, G.; Yufit, D. S.; Howard, A. A. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2788. (c) Chambers, R. D.; Hoskin, P. R.; Kenwright, A. R.; Richmond, P.; Sandford, G.; Yufit, M. S.; Howard, J. A. K. *Org. Biomol. Chem.* **2003**, *1*, 2137.
22. (a) Schmidt, A.; Mordhorst, T.; Nieger, M. *Org. Biomol. Chem.* **2005**, *3*, 3788. (b) Schmidt, A.; Mordhorst, T.; Habeck, T. *Org. Lett.* **2002**, *4*, 1375.
23. Schmidt, A.; Mordhorst, T. *Synthesis* **2005**, 781.
24. Schmidt, A.; Mordhorst, T. *Z. Naturforsch.* **2005**, *60b*, 683.
25. Johnston, H. (Dow Chemical Co.). U.S. Patent 3,549,647; *Chem. Abstr.* **1971**, *75*, 5715.
26. Kyriacou, D. (Dow Chemical Co.). U.S. Patent 3,829,430; *Chem. Abstr.* **1975**, *82*, 43181.
27. Gilmore, C. J.; MacNicol, D. D. *Tetrahedron Lett.* **1984**, *25*, 4303.
28. Johnston, H. (Dow Chemical Co.). U.S. Patent 3,364,223; *Chem. Abstr.* **1968**, *69*, 27254.
29. (a) Ugryumov, E. P.; Kaklyugin, V. Y. *Agrokhimiya* **1995**, *2*, 73. *Chem. Abstr.* **1995**, *122*, 308690. (b) Kukhar, V. P.; Cherepenko, T. I.; Pavlenko, A. F. *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol., Khim. Biol. Nauki* **1982**, *12*, 60. *Chem. Abstr.* **1983**, *98*, 121208. (c) Dzyuban, A. D.; Protopopova, G. V.; Reidalova, L. I.; Sologub, S. L.; Zalesskii, G. A.; Moshchitskii, S. D.; Pavlenko, A. F. *Fiziol. Akt. Veshchestva* **1974**, *6*, 76. *Chem. Abstr.* **1975**, *82*, 165834.
30. Xu, X.; Qian, X.; Li, Z.; Song, G. *J. Fluorine Chem.* **1998**, *88*, 9.
31. (a) Efremov, I. V.; Sipyagin, A. M.; Pomytkin, I. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1996**, *32*, 796. (b) Boehme, H.; Ahrens, G. *Liebigs Ann. Chem.* **1982**, *6*, 1030. (c) Tominaga, Y. *Chem. Pharm. Bull.* **1977**, *25*, 1519.
32. Yamanouchi Pharm., DE 2727686, 1978; *Chem. Abstr.* **1978**, *88*, 136637.
33. Phillips, G. B.; Buckman, B. O.; Davey, D. D.; Eagen, K. A.; Guilford, W. J.; Hinchman, J.; Ho, E.; Koovakkat, S.; Liang, A.; Light, D. R.; Mohan, R.; Ng, H. P.; Post, J. M.; Shaw, K. J.; Smith, D.; Subramanyam, B.; Sullivan, M. E.; Trinh, L.; Vergona, R.; Walters, J.; White, K.; Whitlow, M.; Wu, S.; Xu, W.; Morrissey, M. M. *J. Med. Chem.* **1998**, *41*, 3557.
34. (a) Sell, W. J.; Dootson, F. W. *J. Chem. Soc.* **1897**, *71*, 1082. (b) Sell, W. J.; Dootson, F. W. *J. Chem. Soc.* **1898**, *73*, 441.
35. Chen, T. K.; Flowers, W. T. *J. Chem. Soc., Chem. Commun.* **1980**, *23*, 1139.
36. Sheldrick, G. M. *SHELXS-97, Acta Crystallogr., Sect. A* **1990**, *46*, 467.
37. Sheldrick, G. M. *SHELXL-97*, University of Göttingen: Göttingen, Germany, 1997.