Syntheses and Properties of Di- and Tricationic Hetarenium-Substituted Pyrimidines*

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2,4-Dichloro-, 4,6-dichloro-, 2,4,6-trichloro- and tetrachloropyrimidine undergo nucleophilic displacements by 4-(dimethylamino)pyridine to give (pyrimidine-2,4-diyl)-1,1'-bis[4-(dimethylamino)pyridinium] dichloride, (pyrimidine-4,6-diyl)-1,1'-bis[4-(dimethylamino)-pyridinium] dichloride, (pyrimidine-2,4,6-triyl)-1,1',1"-tris[4-(dimethylamino)pyridinium] trichloride, and (5-chloropyrimidine-2,4,6-triyl)-1,1',1"-tris[4-(dimethylamino)pyridinium] trichloride, respectively. Nucleophilic substitutions of the pyridinium substituents by O- and S-nucleophiles to functionalized pyrimidines are examined.

Key words: Nucleophilic Substitution, Thioethers, DMAP, Chloropyrimidines

Introduction

Hetarenium compounds are interesting molecules both from biological and chemical points of view. Numerous primary and secondary metabolites, among them oligocationic, cationic, neutral, and anionic alkaloids possess the pyridinium ring. Thus, the biologically active pyridinium alkaloid **1** from the Micronesian sponge *Callyspongia fibrosa* is an example of oligocationic species from natural sources [1] (Scheme 1). Cyclostellettamine **2** from the marine sponge *Stelletta maxima* [2, 3], a potential muscarin receptor antagonist, is a dicationic molecule. The mesomeric betaines, such as pyridinium phenolate **3** from the leaves of *Punica granatum* [4, 5] and the collagen cross-link Deoxypyridinoline **4** [6], are neutral natural products due to their even number of positive and negative charges within the same molecule. In general, heterocyclic mesomeric betaines are divided into four major classes depending on their type of conjugation, *i.e.* in conjugated mesomeric betaines – including 1,2-dipoles as a subclass –, cross-conjugated, as well as pseudo-cross-conjugated systems [7, 8]. 1-Carboxymethylnicotinic acid **5**, which was isolated from the marine sponge *Anthosigmella cf. raromicrosclera* [9], is an anionic pyridinium alkaloid due to partial structures of a cross-conjugated heterocyclic mesomeric betaine plus one additional carboxylate group.

In organic chemistry, heteroarenium substituents are able to stabilize reactive anionic species such as the allyl anion [10], uracilates [11, 12], pyrimidinium-olates [13 – 15], pyrimidinium-aminides [16, 17], and pyridinium-olates [18], or radical species such as the allyl radical [19]. Furthermore, polycationic heteroarenium compounds were prepared as organic oxidants [20]. We found that poly-halogenated pyridines can be converted regioselectively into mono-, tri-, penta-, and decacationic species as exemplified by **6** – **9** in Scheme 2. Thus, nucleophilic heteroaromatics regioselectively exchange the 4-position of pentachloropyridine to form **6** [21]. In contrast to aliphatic nitrogen nucleophiles, no mixtures of 2- and 4-substituted products are obtained. Slightly more vigorous reaction conditions give the tricationic species **7** which can be substituted by one type ($R^1 = R^2$) or two types of heteroaromatics ($R^1 \neq R^2$). Interception of the leaving group by trifluorosulfonic acid trimethylsilylester (TMSOTf) at high temperatures results in the formation of pentacations such as **8**. The 4-amino derivative of **8** (R = NH_2) can be protonated to yield a decacationic molecule **9** [21].

Hetarenium-substituted pyridines proved to be versatile starting materials for the regioselective syn-

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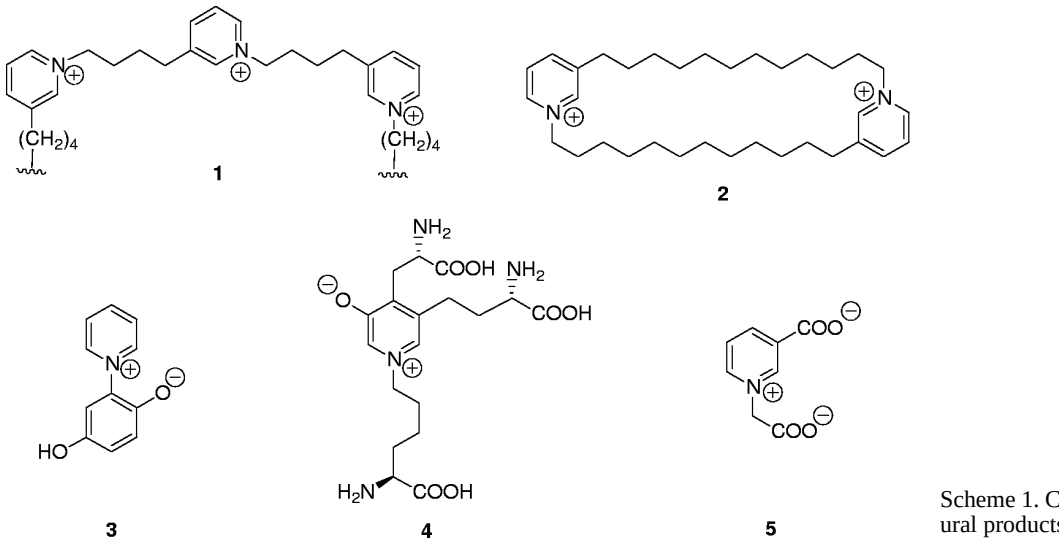
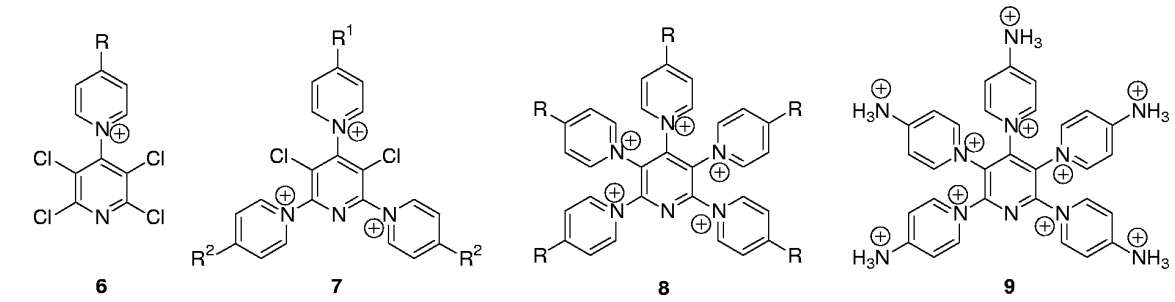


Scheme 1. Charges in natural products.



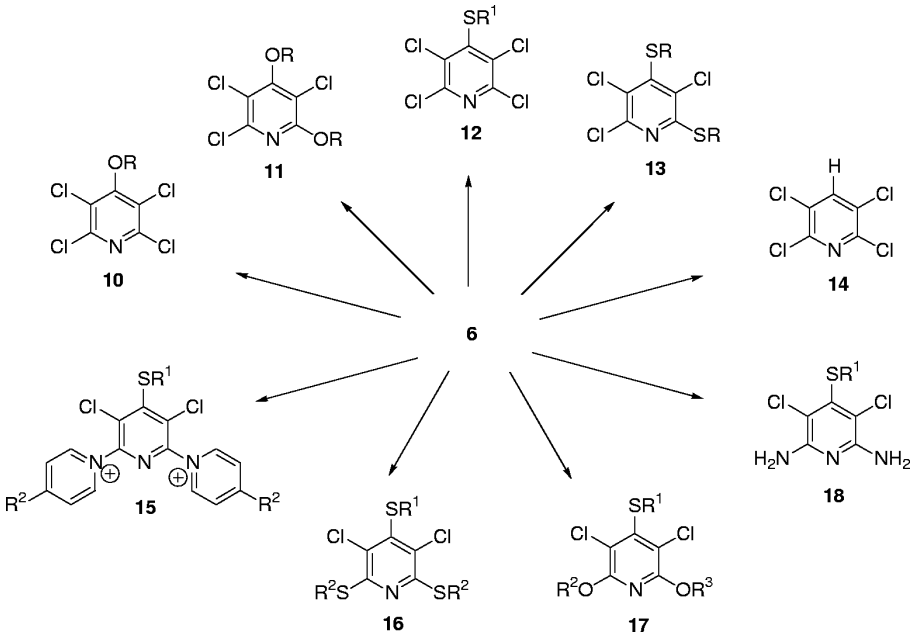
Scheme 2. Heteroarenium-substituted pyridines.

thesis of highly substituted pyridines such as pyridine ethers [22], thioethers [23], and amines [24]. A small part of a broad variety of possible syntheses is presented in Scheme 3. As an example, the monocationic hetarenium salt **6** can be converted into the pyridines **10**–**14** which are again starting materials for additional transformations. Thus, the 2,3,5,6-tetrachloro-4-sulfanylpyridines **12** react to the bis-hetarenium salts **15**, which form biologically interesting S^2,Cl^3,S^4,Cl^5,S^6-pentasubstituted pyridines **16** [23], or symmetric ($R^2 = R^3$) and non-symmetric ($R^2 \neq R^3$) O^2,Cl^3,S^4,Cl^5,O^6-pentasubstituted pyridines **17**. Analogously, first representatives of N^2,Cl^3,S^4,Cl^5,N^6-pentasubstituted pyridines **18** were prepared *via* **12** and **15** [24]. Similarly, a broad variety of reactions starting from the tricationic heteroarenium salt **7** is possible, leading to hitherto unavailable highly substituted pyridines with O^2,Cl^3,O^4,Cl^5,O^6- [22] or S^2,Cl^3,S^4,Cl^5,S^6-substitution pattern [23].

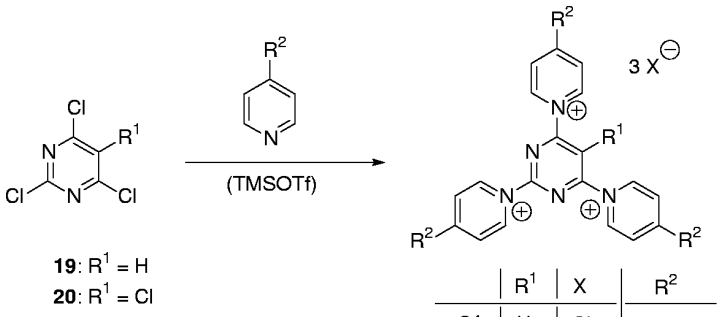
In continuation of earlier work [25–27] we report here the application of this synthetic strategy to the pyrimidine ring system. We present the syntheses of di- and tricationic hetarenium-substituted pyrimidines and our first results of studies directed toward the synthetic potential of the resulting pyrimidine-hetarenium salts in nucleophilic displacement reactions with O- and S-nucleophiles.

Results and Discussion

4-(Dimethylamino)pyridine, 4-aminopyridine, and 4-(pyrrolidin-1-yl)pyridine exchange the 2-, 4-, and 6-chloro substituents of 2,4,6-trichloropyrimidine **19** and 2,4,5,6-tetrachloropyrimidine **20**, respectively, to give the (pyrimidine-2,4,6-triyl)-1,1',1"-trispyridinium trichlorides **21**–**25** and **27**–**29** in fair to excellent yields (Scheme 4). Neither the formation of mono- nor of dicationic molecules were observed. Best yields were obtained when the reaction of tetrachloro-



Scheme 3. Synthetic potential of heteroarenium-substituted pyridines.



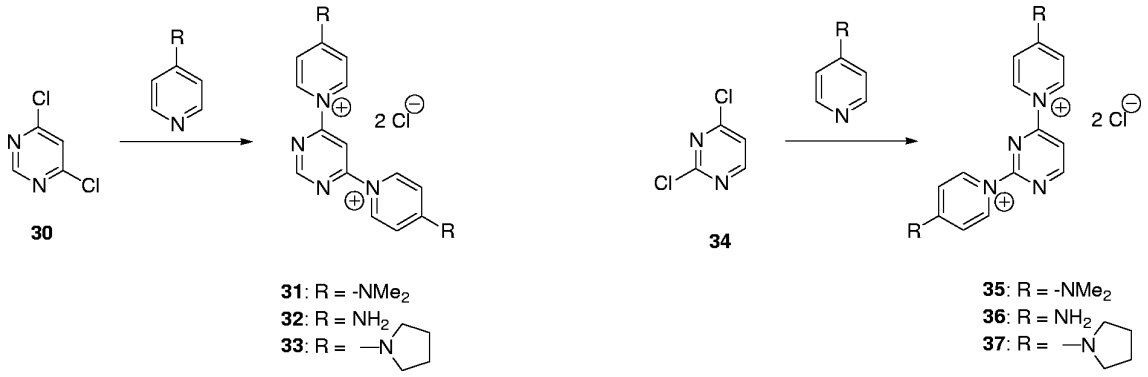
	R^1	X	R^2
21	H	Cl	-NMe_2
22	Cl	Cl	
23	Cl	OTf	
24	H	Cl	-NH_2
25	Cl	Cl	
26	Cl	OTf	
27	H	Cl	—N
28	Cl	Cl	
29	Cl	OTf	

Scheme 4. Formation of hetarenium-substituted pyrimidines.

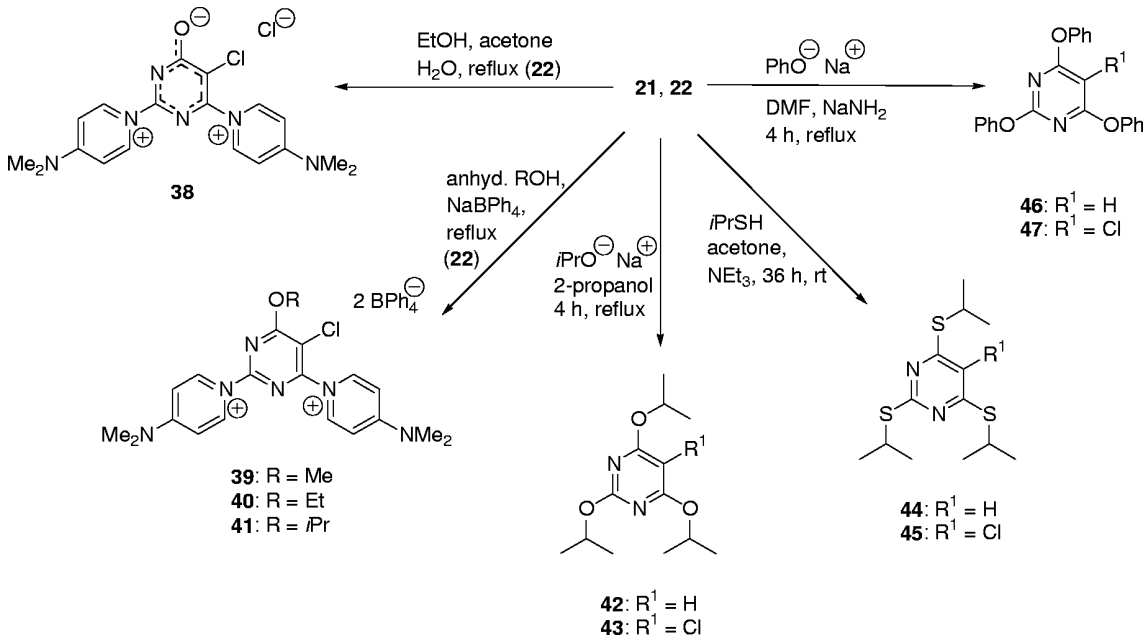
pyridine **20** with the heteroaromatics was conducted in DMF in the presence of stoichiometric amounts of TMSOTf to intercept the leaving group as TMSCl and to form the triflates **23** and **29**; however, fourfold substitution to a tetracationic species was not observed under these reaction conditions. On trying to prepare **26** following this procedure decomposition occurred.

Reaction of 4,6-dichloropyrimidine **30** with 4-(dimethylamino)pyridine, 4-aminopyridine, and 4-(pyrrolidin-1-yl)pyridine, respectively, resulted in the formation of the dicationic hetarenium salts **31**–**33**. Correspondingly, 2,4-dichloropyrimidine **34** gave **35**–**37** in quantitative yields, respectively (Scheme 5).

We next tested some substitution reactions on the heteroaromatics. As reported earlier, the trication **22** – as well as its pyridinium derivative (R^2 = H) [14] – reacts with water to form the tripole **38** [13] (Scheme 6). Anhydrous alcohols in the

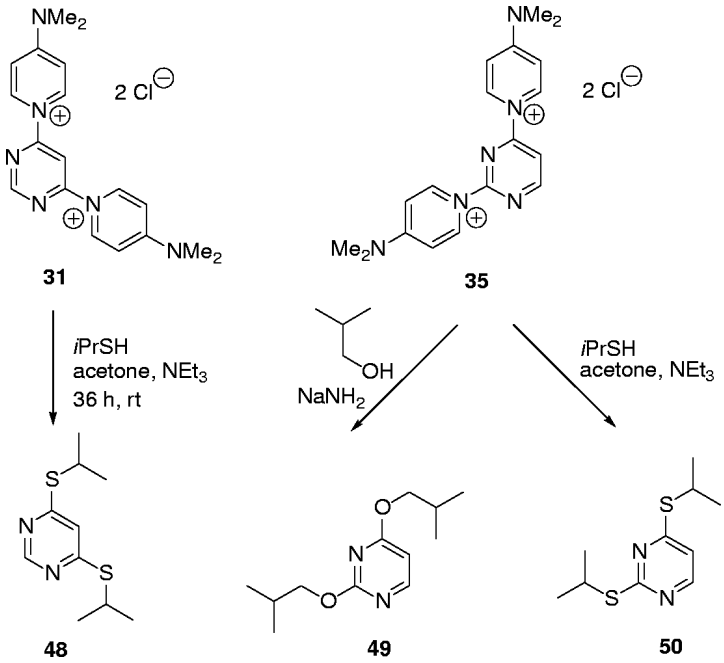


Scheme 5. Dicationic species.

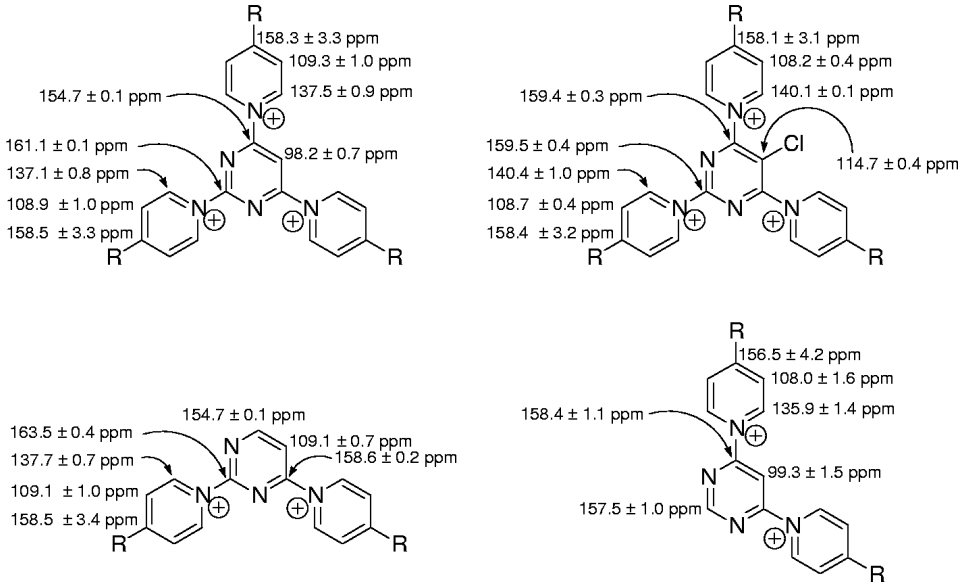


Scheme 6. Synthetic potential of pyridinium-substituted pyrimidines.

presence of sodium tetraphenylborate convert the trication **22** to the 4-alkoxy-substituted bis-hetarenium salts **39**–**41** [13, 27]. Applying modified reaction condition gives rise to the formation of the new compound 2,4,6-tri(2-propoxy)pyrimidine **42** starting from **21** and sodium 2-propanolate in 2-propanol. Surprisingly, 2,4,6-trialkoxy-substituted pyrimidines are quite scarcely described species. 2,4,6-Trimethoxypyrimidine was prepared earlier from 2,4,6-trichloropyrimidine [28, 29]. Alternative procedures start from 4-chloro-2,6-dimethoxy-pyrimidine [30, 31] or pyrimidine-2,4,6-trione [32]. Some derivatives of 2-alkoxy-4,6-dimethoxy-substituted pyrimidines were prepared from 2-(methylsulfonyl)-4,6-dimethoxypyrimidine as orally active nonpeptidic Endothelin A receptor antagonists [33]. The 5-chloro-substituted trication **22** gives **43** under analogous reaction conditions, which is – to the best of our knowledge – the first representative of a O^2,O^4,Cl^5,O^6-tetrasubstituted pyrimidine. 2-Propanthiol as nucleophile replaces the hetarenium substituents of **21** and **22** to yield the sulfanyl-substituted pyrimidines **44** and **45**. Some derivatives of **44** and **45** are literature-known; they were synthesized by multi-step-procedures as potentially pharmacologically active compounds [34–36]. The 2,4,6-triphenoxypyrimidine **46** is a known compound [37], but



Scheme 7. Nucleophilic displacement reactions on dicationic pyrimidines.



Scheme 8. Peak assignments of the ^{13}C NMR resonance frequencies.

its 5-chloro substituted derivative **47** – formed on treatment of **22** with phenolate – has never been described to the best of our knowledge.

No reaction was observable on treatment of the dication **31** with sodium 2-propanolate in 2-propanol; 2-propanthiol in acetone in the presence of triethylamine, however, yielded the 4,6-disulfanyl-substituted pyrimidine **48** in low yields as a new representative of the very scarcely described class of S^4,S^6-disulfanyl-substituted pyrimidines [38 – 41] (Scheme 7); some of these were prepared starting from dichloropyrimidine **30** [38]. Better results were obtained starting from dication **35** which gave the 2,4-dialkoxypyrimidine **49** on reaction with *iso*-butanol in the presence of sodium amide. 2-Propanethiol as nucleophile formed pyrimidine **50** in 78% yield on reaction

with **35**. O^2,O^4- and S^2,S^4-disubstituted pyrimidines are well-known; the latter mentioned class of compounds is available *inter alia* starting from 1*H*-pyrimidine-2,4-dione [42 – 46].

In the NMR spectra taken in D_2O or D_2O/[D_6]-DMSO-mixtures, the α-hydrogen atoms of the pyridinium rings in **21**, **24**, and **27** appear at $\delta = 9.19 \pm 0.02$ ppm and 8.89 ± 0.04 ppm in a 1 : 2 ratio. The corresponding β-hydrogen atoms give resonance frequencies at $\delta = 7.00 \pm 0.08$ and 7.02 ± 0.10 ppm. The chlorine at C-5 of the pyridinium ring causes an upfield shift of the hydrogens of the pyridinium rings of **22**, **23**, **25**, **28**, and **29**. Thus, the α-hydrogen atoms appear at $\delta = 9.00 \pm 0.20$ ppm/8.41 ± 0.22 ppm in a 1 : 2 ratio, while the corresponding β-hydrogen atoms give signals at $\delta = 6.95 \pm 0.12$ ppm and 6.92 ± 0.12 ppm, respectively. Peak assignments of the ^{13}C NMR resonance frequencies are shown in Scheme 8.

In summary, we present here the syntheses of hetarenium-substituted pyrimidines and some expeditious approaches for the preparation of functionalized pyrimidines which might be of interest in bio-organic or medicinal chemistry.

Experimental Section

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. NMR data of all compounds are presented unless they are described in the literature. The numbering C-2 to C-6 and 2-H to 6-H refers to the pyrimidine ring, whereas C-α/α-H and C-β/β-H are used to describe the corresponding atoms of the pyridinium substituents. FT-IR spectra were obtained on a Bruker Vektor 22 in the range of 400 to 4000 cm^{-1} (2.5% pellets in KBr). Melting points are uncorrected.

General procedure for the synthesis of tricationic salts **21** – **29** *starting from halogenated pyrimidines*

Procedure A for the formation of the chlorides **21**, **22**, **24**, **25**, **27**, *and* **28**: In 200 ml of DMF were dissolved 2,4,6-trichloropyrimidine (1.83 g, 10 mmol) or 2,4,5,6-tetrachloropyrimidine (2.18 g, 10 mmol) and 4-aminopyridine (2.82 g, 30 mmol) or 4-dimethylaminopyridine (3.66 g, 30 mmol) or 4-(pyrrolidin-1-yl)-pyridine (4.44 g, 30 mmol). For a period of one hour the mixture was stirred at 140 °C. During this time the product precipitated as a light solid. After cooling, 100 ml of ethyl acetate were added to the reaction mixture and the solids were filtered off, washed with ethyl acetate and dried *in vacuo*.

Procedure B for the formation of the triflates **23** *and* **29**: In 200 ml of 1,2-dichlorobenzene 2,4,5,6-tetrachloropyrimidine (2.18 g, 10 mmol), trifluoromethanesulfonic acid trimethylsilylester (8.89 g, 40 mmol) and 4-(dimethylamino)pyridine (3.66 g, 30 mmol), or 4-(pyrrolidin-1-yl)-pyridine (4.44 g, 30 mmol), were dissolved. For a period of three hours the mixture was heated at reflux temperature. During this time the product precipitated as a light solid. After cooling, 100 ml of ethyl acetate were added to the reaction mixtures and the resulting solids were filtered off, washed with ethyl acetate and dried *in vacuo*.

(Pyrimidine-2,4,6-triyl)-1,1',1"-tris[4-(dimethylamino)pyridinium] trichloride (**21**)

All data are in agreement to those reported earlier [25].

(5-Chloropyrimidine-2,4,6-triyl)-1,1',1"-tris[4-(dimethylamino)pyridinium] trichloride (***22***)

M. p. 142 °C. – ^{1}H NMR (200 MHz, D_2O): $\delta = 8.81$ (d, $^3J = 8.1$ Hz, 2H, α-H), 8.24 (d, $^3J = 7.5$ Hz, 4H, α-H), 6.84 (d, $^3J = 7.5$ Hz, 4H, β-H), 6.81 (d, $^3J = 8.1$ Hz, 2H, β-H), 3.08 (s, 18H, CH_3). – ^{13}C NMR (50 MHz, D_2O): $\delta = 159.7$, 159.5 (2 signals overlapped), 158.1, 157.5, 139.4, 139.2, 114.7, 108.3, 107.8, 40.9, 40.8 ppm. – IR (KBr): $\nu =$ 3383, 3054, 1644, 1572, 1381, 1322, 1226, 1158, 829 cm^{-1}. – $C_{25}H_{30}Cl_4N_8 \cdot 6\ H_2O$ (584.37): calcd. C 43.36, H 6.11, N 16.18; found C 43.56, H 6.01, N 16.44.

(5-Chloropyrimidine-2,4,6-triyl)-1,1',1"-tris[4-(dimethylamino)pyridinium] tris(trifluoromethanesulfonate) (**23**)

M. p. 269 °C. – ^{1}H NMR (200 MHz, D_2O): $\delta = 9.03$ (d, $^3J = 7.8$ Hz, 2H, α-H), 8.44 (d, $^3J = 7.8$ Hz, 4H, α-H), 7.06 (d, $^3J = 7.8$ Hz, 4H, β-H), 7.03 (d, $^3J = 7.8$ Hz, 2H, β-H), 3.30 (s, 18H, CH_3) ppm. – ^{13}C NMR (50 MHz, D_2O): $\delta =$ 159.7 (overlapped signals), 158.1, 157.5, 139.4, 136.1, 119.6 ($J = 319.2$ Hz), 114.5, 108.6, 107.9, 40.4 ppm. – IR (KBr): $\nu = 3098$, 1659, 1570, 1500, 1386, 1343, 1260, 1224, 1168, 1030, 830 cm^{-1}. – $C_{28}H_{30}ClF_9N_8O_9S_3$(925.16): calcd. C 36.35, H 3.27, N 12.11; found C 35.94, H 2.98, N 12,01.

(Pyrimidine-2,4,6-triyl)-1,1',1"-tris(4-aminopyridinium) trichloride (**24**)

M. p. 328 °C. – ^{1}H NMR (200 MHz, D_2O): $\delta = 9.17$ (d, $^3J = 7.9$ Hz, 2H, α-H), 8.86 (d, $^3J = 7.8$ Hz, 4H, α-H), 8.26 (s, 1H, 5-H), 7.01 (d, $^3J = 7.9$ Hz, 2H, β-H), 6.96 (d, $^3J =$ 7.8 Hz, 4H, β-H) ppm. – ^{13}C NMR (50 MHz, D_2O): $\delta =$ 161.7, 161.6, 161.5, 154.7, 138.4, 137.9, 110.2, 109.8 ppm. – IR (KBr): $\nu = 3041$, 1672, 1588, 1532, 1459, 1374, 1317, 1248, 1197, 1145 cm^{-1}. – $C_{19}H_{19}Cl_3N_8 \cdot 1.5\ H_2O$ (465.77): calcd. C 46.31, H 4.50, N 22.74; found C 46.37, H 4.44, N 22.91.

(5-Chloropyrimidine-2,4,6-triyl)-1,1',1"-tris(4-aminopyridinium) trichloride (**25**)

M. p. 181 °C. – ^{1}H NMR (200 MHz, D_2O/[D_6]-DMSO = 1 : 1): δ = 9.17 (d, ^3J = 7.7 Hz, 2H, α-H), 8.63 (d, ^3J = 7.2 Hz, 4H, α-H), 7.11 (d, ^3J = 7.2 Hz, 4H, β-H), 7.07 (d, ^3J = 7.7 Hz, 2H, β-H) ppm. – ^{13}C NMR (50 MHz, D_2O/[D_6]-DMSO = 1 : 1): δ = 161.0, 160.4, 159.1 (2 overlapped signals), 141.4, 141.0, 115.1, 109.1, 108.6 ppm. – IR (KBr): ν = 1655, 1573, 1520, 1380, 1323, 1255, 1201, 1160, 845 cm^{-1}. – $C_{19}H_{18}Cl_4N_8 \cdot 5.5\ H_2O$ (500.21): calcd. C 38.08, H 4.88, N 18.70; found C 37.94, H 4.90, N 18.70.

(Pyrimidine-2,4,6-triyl)-1,1'-1"-tris[4-(pyrrolidin-1-yl)pyridinium] trichloride (**27**)

All spectroscopic data are in agreement to those reported earlier [25].

(5-Chloropyrimidine-2,4,6-triyl)-1,1',1"-tris[4-(pyrrolidin-1-yl)pyridinium] trichloride (***28***)

M. p. 66 °C. – ^{1}H NMR (200 MHz, D_2O): δ = 9.00 (d, ^3J = 8.1 Hz, 2H, α-H), 8.41 (d, ^3J = 7.8 Hz, 4H, α-H), 6.91 (d, ^3J = 7.8 Hz, 4H, β-H), 6.95 (d, ^3J = 8.1 Hz, 2H, β-H), 3.50 – 3.80 (m, 12H, pyrrolidine), 1.90 – 2.20 (m, 12H, pyrrolidine) ppm. – ^{13}C NMR (50 MHz, D_2O): δ = 159.8, 159.7, 155.1, 154.5, 139.3, 139.1, 114.3, 108.4*, 49.6*, 24.6* ppm (* 2 signals overlapped). – ESIMS: m/z = 338 (M-Cl, 100%). – IR (KBr): ν = 3046, 1650, 1573, 1409, 1208, 1166, 1047 cm^{-1}. – $C_{31}H_{36}Cl_4N_8 \cdot 7\ H_2O$ (662.29): calcd. C 47.21, H 6.39, N 14,21, found C 47.06, H 5.73, N 13.79.

(5-Chloropyrimidine-2,4,6-triyl)-1,1',1"-tris[4-(pyrrolidin-1-yl)pyridinium] tris(trifluoromethanesulfonate) (**29**)

M. p. 189 °C. – ^{1}H NMR (200 MHz, D_2O/[D_6]-DMSO = 1 : 1): δ = 9.23 (d, ^3J = 7.9 Hz, 2H, α-H), 8.73 (d, ^3J = 7.8 Hz, 4H, α-H), 7.24 (d, ^3J = 7.8 Hz, 4H, β-H), 7.13 (d, ^3J = 7.9 Hz, 2H, β-H), 3.69 – 3.81 (m, 12H, pyrrolidine), 2.00 – 2.20 (m, 12H, pyrrolidine) ppm. – ^{13}C NMR (50 MHz, D_2O/[D_6]-DMSO = 1 : 1): δ = 158.8*, 154.4, 153.9, 139.7, 139.0, 120.5 (J = 321.8 Hz), 115.3, 110.9, 109.0, 108.7, 49.7* (pyrrolidine), 24.5* (pyrrolidine) ppm (* 2 signals overlapped). – IR (KBr): ν = 3547, 3483, 3092, 1658, 1571, 1412, 1385, 1342, 1224, 1166, 1029 cm^{-1}. – $C_{34}H_{36}ClF_9N_8O_9S_3 \cdot 3\ H_2O$ (1003.33): calcd. C 38.62, H 4.00, N 10.60; found C 38.75, H 4.04, N 10.71.

General procedure for the synthesis of dicationic salts **31** – **33**

In 200 ml of DMF 2,4-dichloropyrimidine (1.49 g, 10 mmol) or 4,6-dichloropyrimidine (1.49 g, 10 mmol) and 4-aminopyridine (1.88 g, 20 mmol) or 4-(dimethylamino)pyridine (2.44 g, 20 mmol) or 4-(pyrrolidin-1-yl)pyridine (2.96 g, 20 mmol) were dissolved. For a period of one hour the mixture was stirred at 140 °C. During this time the product precipitated as a light yellow solid. After cooling, 100 ml of ethyl acetate were added to the reaction mixtures and the solids were filtered off, washed with ethyl acetate and dried *in vacuo*.

(Pyrimidine-4,6-diyl)-1,1'-bis[4-(dimethylamino)pyridinium] dichloride (**31**)

M. p. 313 °C. – ^{1}H NMR (200 MHz, [D_6]-DMSO/D_2O = 5 : 1): δ = 9.31 (s, 1H, 2-H), 9.12 (d, ^3J = 7.9 Hz, 4H, α-H), 8.70 (s, 1H, 5-H), 7.28 (d, ^3J = 7.9 Hz, 4H, β-H), 3.39 (s, 12H, CH_3) ppm. – ^{13}C NMR (50 MHz, [D_6]-DMSO/D_2O = 5 : 1): δ = 159.2, 158.5, 157.2, 137.2, 108.0, 100.6, 40.6 ppm. – IR (KBr): ν = 3416, 3055, 1650, 1571, 1464, 1386, 1348, 1260, 1178, 1088, 1051, 835 cm^{-1}. – $C_{18}H_{22}Cl_2N_6 \cdot 1,5\ H_2O$ (393.32): calcd. C 51.53, H 5.99, N 19.99; found C 51.98, H 5.61, N 20.02.

(Pyrimidine-4,6-diyl)-1,1'-bis(4-aminopyridinium) dichloride (**32**)

M. p. 314 °C. – ^{1}H NMR (200 MHz, [D_6]-DMSO/D_2O = 1 : 1): δ = 9.25 (s, 1H, 2-H), 8.94 (d, ^3J = 7.9 Hz, 4H, α-H), 8.37 (s, 1H, 5-H), 7.08 (d, ^3J = 7.9 Hz, 4H, β-H) ppm. – ^{13}C NMR (50 MHz, [D_6]-DMSO/D_2O = 1 : 1): δ = 160.7, 159.5, 158.5, 138.4, 109.6, 100.6 ppm. – IR (KBr): ν = 2986, 1650, 1579, 1467, 1245, 1194, 1087, 830, 779 cm^{-1}. – $C_{14}H_{14}Cl_2N_6 \cdot 1\ H_2O$ (337.18): calcd. C 47.34, H 4.54, N 23.66; found C 47.51, H 3.72, N 23.63.

(Pyrimidine-4,6-diyl)-1,1'-bis[4-(pyrrolidin-1-yl)pyridinium] dichloride (**33**)

M. p. 272 °C. – ^{1}H NMR (200 MHz, [D_6]-DMSO/D_2O = 1 : 1): δ = 9.13 (s, 1H, 2-H), 8.83 (d, ^3J = 7.9 Hz, 4H, α-H), 8.24 (s, 1H, 5-H), 6.97 (d, ^3J = 7.9 Hz, 4H, β-H), 3.55 – 3.75 (m, 8H, pyrrolidine), 2.00 – 2.15 (m, 8H, pyrrolidine) ppm. – ^{13}C NMR (50 MHz, [D_6]-DMSO/D_2O = 1 : 1): δ = 157.4, 156.4, 152.3, 134.5, 106.4, 97.8, 47.0, 22.1 ppm. – IR (KBr): ν = 3444, 3039, 1652, 1570, 1468, 1342, 1204, 1082, 837 cm^{-1}. – $C_{23}H_{26}Cl_2N_6 \cdot 3,5\ H_2O$ (445.80): calcd. C 53.88, H 6.37, N 17.14; found C 54.17, H 5.83, N 17.10.

(Pyrimidine-2,4-diyl)-1,1'-bis[4-(dimethylamino)pyridinium] dichloride (**35**)

M. p. 269 °C. – ^{1}H NMR (200 MHz, D_2O): δ = 9.12 (d, ^3J = 8.2 Hz, 2H, α-H), 9.00 (d, ^3J = 5.8 Hz, 1H, 6-H), 8.85 (d, ^3J = 8.2 Hz, 2H, α-H), 7.88 (d, ^3J = 5.8 Hz, 1H, 5-H), 7.08 (d, ^3J = 8.2 Hz, 2H, β-H), 7.04 (d, ^3J = 8.2 Hz, 2H, β-H), 3.32 (s, 6H, CH_3), 3.30 (s, 6H, CH_3) ppm. – ^{13}C NMR (50 MHz, D_2O): δ = 163.0, 158.4, 158.0, 157.9,

154.6, 136.6, 136.5, 108.9, 108.2, 107.7, 40.5, 40.4 ppm. – IR (KBr): ν = 3450, 3048, 1649, 1592, 1447, 1383, 1350, 1293, 1219, 1129, 1105 cm^{-1}. – $C_{18}H_{22}Cl_2N_6 \cdot 3\,H_2O$ (393.32): calcd. C 48.33, H 6.31, N 18.79; found C 48.59, H 5.91, N 18.59.

(Pyrimidine-2,4-diyl)-1,1'-bis(4-aminopyridinium) dichloride (**36**)

M. p. 332 °C. – ^{1}H NMR (200 MHz, D_2O): δ = 9.10 (d, ^3J = 8.2 Hz, 2H, α-H), 9.00 (d, ^3J = 5.8 Hz, 1H, 6-H), 8.79 (d, ^3J = 8.2 Hz, 2H, α-H), 7.86 (d, ^3J = 5.8 Hz, 1H, 5-H), 6.95 (d, ^3J = 8.2 Hz, 2H, β-H), 6.91 (d, ^3J = 8.2 Hz, 2H, β-H) ppm. – ^{13}C NMR (50 MHz, D_2O): δ = 163.1, 161.4, 161.3, 158.8, 154.7, 136.3, 138.0, 110.1, 109.6, 109.5 ppm. – IR (KBr): ν = 2955, 1649, 1575, 1448, 1398, 1338, 1285, 1183, 1128, 829 cm^{-1}. – $C_{14}H_{14}Cl_2N_6 \cdot 1\,H_2O$ (337.18): calcd. C 47.34, H 4.54, N 23.66; found C 47.46, H 3.63, N 23.69.

(Pyrimidine-2,4-diyl)-1,1'-bis[4-(pyrrolidin-1-yl)pyridinium] dichloride (***37***)

M. p. 239 °C. – ^{1}H NMR (200 MHz, D_2O): δ = 9.10 (d, ^3J = 8.2 Hz, 2H, α-H), 8.98 (d, ^3J = 5.8 Hz, 1H, 6-H), 8.81 (d, ^3J = 8.2 Hz, 2H, α-H), 7.83 (d, ^3J = 5.8 Hz, 1H, 5-H), 6.93 (d, ^3J = 8.2 Hz, 2H, β-H), 6.89 (d, ^3J = 8.2 Hz, 2H, β-H), 3.50 – 3.75 (m, 8H, pyrrolidine), 1.95 – 2.15 (m, 8H, β-H, pyrrolidine) ppm. – ^{13}C NMR (50 MHz, D_2O): δ = 163.9, 158.6, 155.1, 154.9, 154.7, 136.4, 136.3, 108.9, 108.8, 108.4, 49.7, 49.5, 24.6 (overlapped) ppm. – IR (KBr): ν = 3385, 3055, 1650, 1578, 1446, 1397, 1344, 1293, 1210, 1127 cm^{-1}. – $C_{23}H_{26}Cl_2N_6 \cdot 4\,H_2O$ (445.80): calcd. C 51.06, H 6.62, N 16.24; found C 50.73, H 6.30, N 16.06.

General procedure for the synthesis of 2,4,6-trialkoxypyrimidines **42** *and* **43**

Sodium 2-propanolate (4.11 g, 50 mmol) and salt **21** (5.50 g, 10 mmol) or **22** (5.84 g, 10 mmol) were dissolved in 150 ml of 2-propanol and heated at reflux temperature over a period of four hours. After cooling the alcohol was distilled off *in vacuo* and the residue was filtered through silica gel (EtOAc/petroleum ether = 1/2).

2,4,6-Tri-(2-propoxy)pyrimidine (**42**)

Colorless oil. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.56 (s, 1H, 5-H), 5.15 – 5.35 (m, 3H, C*H*), 1.38 (d, ^3J = 6.2 Hz, 6H, CH_3), 1.32 (d, ^3J = 6.2 Hz, 12H, CH_3) ppm. – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.9, 164.0, 84.4, 69.0, 69.9, 22.0 (overlapped signals) ppm. – IR (NaCl): ν = 1590, 1401, 1316, 1175, 1108, 1051, 905, 813 cm^{-1}. – GC-MS: m/z = 255 (M, 10), 239 (M – CH_3, 100), 212 (M – C_3H_7, 17), 128 (M – 3 C_3H_7, 98). – $C_{13}H_{22}N_2O_3$ (254.12): calcd. C 61.39, H 8.72, N 11.01; found C 60.57, H 8.59, N 10.41.

2,4,6-Tri-(2-propoxy)-5-chloropyrimidine (**43**)

Pale yellow oil. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.37 (h, ^3J = 6.1 Hz, 2H, C*H*), 5.17 (h, ^3J = 6.1 Hz, 1H, C*H*), 1.39 (d, ^3J = 6.1 Hz, 6H, CH_3), 1.38 (d, ^3J = 6.1 Hz, 12H, CH_3) ppm. – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.1, 160.7, 92.3, 70.6, 70.5, 22.0, 21.8 ppm. – IR (NaCl): ν = 2982, 2935, 1569, 1409, 1319, 1129, 1104, 1047 cm^{-1}. – GC-MS: m/z = 289 (M, 100), 246 (M – C_3H_7, 18). – $C_{13}H_{21}ClN_2O_3$(288.77): cald. C 54.07, H 7.33, N 9.70; found C 53.83, H 6.87, N 9.79.

General procedure for the synthesis of the 2,4,6-trialkylsulfanyl-pyrimidines **44** *and* **45**

In 150 ml of acetone were given triethylamine (5.00 g, 0.05 mol), the salt **21** (5.50 g, 10 mmol) or **22** (5.84 g, 10 mmol). At r. t. 2-propanthiol (2.29 g, 30 mmol) was added to this suspension. After 36 h the acetone was distilled off *in vacuo* and the residue was filtered through silica gel (EtOAc/petroleum ether = 1/2).

2,4,6-Tri-(2-propylsulfanyl)pyrimidine (**44**)

Colorless oil. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.58 (s, 1H, 5-H), 4.00 (h, ^3J = 6.9 Hz, 2H, C*H*), 3.91 (h, ^3J = 6.9 Hz, 1H, C*H*), 1.42 (d, ^3J = 6.9 Hz, 6H, CH_3), 1.38 (d, ^3J = 6.8 Hz, 12H, CH_3) ppm. – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.8, 167.8, 110.9, 35.5, 34.5, 23.1, 23.0 ppm. – IR (NaCl): ν = 2964, 2962, 2865, 1521, 1383, 1365, 1266, 1156, 1100, 1055, 842, 816 cm^{-1}. – GC-MS: m/z = 302 (M, 27), 272 (M – 2 CH_3, 100), 227 (M – SC_3H_7, 41), 185 (M – SC_3H_7- C_3H_7, 31). – $C_{13}H_{22}N_2S_3$(302.52): calcd. C 51.61, H 7.33, N 9.26, S 31.80; found C 51.31, H 6.93, N 8.86, S 31.99.

2,4,6-Tri-(2-propylsulfanyl)-5-chloropyrimidine (**45**)

Colorless oil. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.02 (h, ^3J = 6.8 Hz, 2H, C*H*), 3.87 (h, ^3J = 6.9 Hz, 1H, C*H*), 1.43 (d, ^3J = 6.9 Hz, 6H, CH_3), 1.41 (d, ^3J = 6.8 Hz, 12H, CH_3) ppm. – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.3, 165.2, 118.6, 36.0, 35.4, 23.1, 23.0 ppm. – IR (NaCl): ν = 2965, 2865, 1492, 1383, 1365, 1278, 1238, 1155, 1056, 808 cm^{-1}. – GC-MS: m/z = 337 (M, 58), 304 (M – Cl, 100), 261 (M – SC_3H_7, 50). – $C_{13}H_{21}ClN_2S_3$(336.97): calcd. C 46.34, H 6.28, N 8.31, S 28.55; found C 45.64, H 5.88, N 8.01, S 28.09.

General procedure for the synthesis of 2,4,6-triphenoxypyrimidines **46** *and* **47**

Sodium amide (1.30 g, 33 mmol), phenol (2.82 g, 30 mmol) and salt **21** (5.50 g, 10 mmol) or **22** (5.84 g, 10 mmol) were dissolved in 150 ml of DMF and heated at 130 °C for a period of 4 h. After cooling, the DMF was

distilled off *in vacuo* and the residue was filtered through silica gel (EtOAc/petroleum ether = 1/2).

2,4,6-Triphenoxy-5-chloropyrimidine (**47**)

M. p. −47 °C. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.88 – 7.35$ (m, 15H) ppm. – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 166.8, 160.5, 152.4, 152.3, 129.3, 128.8, 125.6, 125.0, 121.5, 121.4, 95.1 ppm. – IR (KBr): $\nu = 3061$, 1562, 1492, 1374, 1209, 1042, 760 cm^{-1}. – GC-MS: $m/z = 391$ (M, 100), 355 (M – Cl, 20). – $C_{22}H_{15}N_2O_3Cl$ (390.80): calcd. C 67.61, H 3.87, N 7.17; found C 66.76, H 3.50, N 7.22.

Synthesis of 2,4-Diisobutylalkoxypyrimidine (**49**)

Sodium amide (1.20 g, 3 mmol) and salt **35** (3.93 g, 10 mmol) were suspended in 150 ml of 2-butanol. Then, the mixture was heated under reflux for 4 hours. After cooling, the alcohol was distilled off *in vacuo* and the residue was filtered through silica gel (EtOAc/petroleum ether = 1/2). Colorless oil. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.15$ (d, $^3J = 5.6$ Hz, 1H, 6-H), 6.35 (d, $^3J = 5.6$ Hz, 1H, 5-H), 4.13 (d, $^3J = 6.8$ Hz, 2H, 4-OCH_2), 4.11 (d, $^3J = 6.8$ Hz, 2H, 2-OCH_2), 2.15 (m, 1H, CH), 2.07 (m, 1H, CH), 1.03 (d, $^3J =$ 6.8 Hz, 6H, 4-CH_3), 0.99 (d, $^3J = 6.8$ Hz, 6H, 2-CH_3) ppm. – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 171.4$, 165.3, 158.2, 101.9, 73.8, 72.6, 27.9, 19.3, 19.2 ppm. – IR (NaCl): $\nu = 2961$, 1585, 1422, 1386, 1338, 1283, 1085, 1015, 815 cm^{-1}. – GC-MS: $m/z = 225$ (MH$^+$, 100), 169 (M – C_4H_9, 18), 113 (M – 2 C_4H_9, 41). – $C_{12}H_{20}N_2O_2$ (224.30): calcd. C 64.26, H 8.99, N 12.49; found C 63.29, H 8.98, N 12.31.

General procedure for the synthesis of the 4,6-dialkylsulfanyl-pyrimidine **48** *and 2,4-dialkylsulfanyl-pyrimidine* **50**

At r. t. the salt **31** (3.93 g, 10 mmol) or **35** (3.93 g, 10 mmol) was suspended in acetone (150 ml) and triethylamine (5.00 g, 0.05 mol). Then, 2-propanethiol (1.53 g, 20 mmol) was added. After 36 h of stirring at rt the acetone was distilled off *in vacuo* and the residue was filtered through silica gel (EtOAc/petroleum ether = 1/2).

4,6-Di-(2-propylsulfanyl)pyrimidine (**48**)

Colorless oil. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.67$ (d, $^5J = 1.3$ Hz, 1H, 2-H), 6.92 (d, $^5J = 1.3$ Hz, 1H, 5-H), 4.00 (h, $^3J = 6.8$ Hz, 2H, CH), 1.40 (d, $^3J = 6.8$ Hz, 12H, CH_3) ppm. – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 168.2$, 157.3, 115.8, 34.6, 23.0 ppm. – IR (NaCl): $\nu = 1543$, 1492, 1428, 1275, 1242, 1156, 1085, 1054, 976, 803 cm^{-1}. – GC-MS: $m/z = 229$ (MH$^+$, 100). – $C_{10}H_{16}N_2S_2$(228.00): calcd. C 52.59, H 7.06, N 12.27; found C 52.53, H 6.71, N 11.34.

2,4-Di-(2-propylsulfanyl)pyrimidine (**50**)

Colorless oil. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.08$ (d, $^3J = 5.4$ Hz, 1H, 6-H), 6.73 (d, $^3J = 5.4$ Hz, 1H, 5-H), 4.06 (h, $^3J = 6.8$ Hz, 1H, 4-CH), 3.93 (h, $^3J = 6.9$ Hz, 1H, 2-CH), 1.43 (d, $^3J = 6.8$ Hz, 6H, CH_3), 1.41 (d, $^3J = 6.9$ Hz, 6H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 171.8$ (C-2), 170.2 (C-2), 154.3 (C-6), 114.2 (C-5), 35.5 (*C*H), 34.5 (*C*H), 23.0 (*C*H$_3$), 22.9 (2 *C*H$_3$) ppm. – IR (NaCl): $\nu = 2964$, 2927, 2866, 1550, 1518, 1404, 1313, 1205, 1151, 1056, 820 cm^{-1}. – GC-MS: $m/z = 228$ (M, 100), 153 (M – C_3H_7S, 11). – $C_{10}H_{16}N_2S_2$ (228.00): calcd. C 52.59, H 7.06, N 12.27; found C 52.47, H 7.12, N 12.25.

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