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 oligocaticonic, 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 oligocaticonic species from natural sources [1] (Scheme 1). Cyclostellettamine 2 from the marine sponge *Stelletta maxima* [2, 3], a potential muscarin receptor antagonist, is a dicatonic 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 *Anthosigemma 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, heteroaarenium 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, polycatonic heteroarenium compounds were prepared as organic oxidants [20]. We found that poly-halogenated pyridines can be converted regioselectively into mono-, tri-, penta-, and decacatonic species as exemplified by 6 – 9 in Scheme 2. Thus, nucleophilic heteroarenoamides 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 (R1 = R2) or two types of heteroaamides (R1 ≠ R2). Interception of the leaving group by trifluorosulfonic acid trimethylsilylster (TMSOTf) at high temperatures results in the formation of pentacations such as 8. The 4-amino derivative of 8 (R = NH2) can be protonated to yield a decacatonic molecule 9 [21].

Hetarenium-substituted pyridines proved to be versatile starting materials for the regioselective syn-
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 heteroarenium 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-heteroarenium salts 15, which form biologically interesting S2,Cl3,S4,Cl5,S6-pentasubstituted pyridines 16 [23], or symmetric (R2 = R3) and non-symmetric (R2 ≠ R3) O2,Cl3,S4,Cl5,O6-penta-substituted pyridines 17. Analogously, first representatives of N2,Cl3,S4,Cl5,N6-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 O2,Cl3,O4,Cl5,O6- [22] or S2,Cl3,S4,Cl5,S6-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 heteroarenium-substituted pyrimidines and our first results of studies directed toward the synthetic potential of the resulting pyrimidine-heteroarenium 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-
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 (R² = 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 tri-cation 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 O2,O4,Cl5,O6-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
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 dichloro-pyrimidine 30 [38]. Better results were obtained starting from dication 35 which gave the 2,4-dialkoxy-pyrimidine 49 in reaction with iso-butanol in the presence of sodium amide. 2-Propanethiol as nucleophile formed pyrimidine 50 in 78% yield on reaction
with 35. O2,O4- and S2,S4-disubstituted pyrimidines are well-known; the latter mentioned class of compounds is available inter alia starting from 1H-pyrimidine-2,4-dione [42–46].

In the NMR spectra taken in D2O or D2O/[D6]-DMSO-mixtures, the α-hydrogen atoms of the pyridinium rings in 21, 24, and 27 appear at δ = 9.19 ± 0.02 ppm and 8.89 ± 0.04 ppm in a 1:2 ratio. The corresponding β-hydrogen atoms give resonance frequencies at δ = 7.00 ± 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 δ = 9.00 ± 0.20 ppm/8.41 ± 0.22 ppm in a 1:2 ratio, while the corresponding β-hydrogen atoms give signals at δ = 6.95 ± 0.12 ppm and 6.92 ± 0.12 ppm, respectively. Peak assignments of the 13C NMR resonance frequencies are shown in Scheme 8.

In summary, we present here the syntheses of hetareniun-stibuted 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 1H and 13C 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), 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.

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 trimethylsilyl ester (8.89 g, 40 mmol) and 4-(dimethylamino)pyrididine (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)pyridinum] trichloride (21)

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

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

M. p. 142 °C – 1H NMR (200 MHz, D2O): δ = 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, CH₃). – 13C NMR (50 MHz, D2O): δ = 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): v = 3383, 3054, 1618, 1588, 1532, 1459, 1374, 1317, 1260, 1224, 1168, 829 cm⁻¹. – C25H30Cl4N8·2.5H₂O (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)pyridinum] tris(trifluoromethanesulfonate) (23)

M. p. 269 °C – 1H NMR (200 MHz, D2O): δ = 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, CH₃). – 13C NMR (50 MHz, D2O): δ = 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): v = 3098, 1659, 1570, 1500, 1386, 1343, 1260, 1224, 1168, 1030, 830 cm⁻¹. – C25H30Cl4F9N8O9S3 (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-aminopyridinum)trichloride (24)

M. p. 328 °C – 1H NMR (200 MHz, D2O): δ = 9.17 (d, 3J = 7.8 Hz, 2H, α-H), 8.86 (d, 3J = 7.8 Hz, 4H, α-H), 8.26 (s, 1H, 5-H), 7.01 (d, 3J = 7.8 Hz, 2H, β-H), 6.96 (d, 3J = 7.8 Hz, 4H, β-H) ppm. – 13C NMR (50 MHz, D2O): δ = 161.7, 161.6, 161.5, 154.7, 138.4, 137.9, 110.2, 109.8 ppm. – IR (KBr): v = 3041, 1672, 1588, 1532, 1459, 1374, 1317, 1248, 1197, 1145 cm⁻¹. – C19H19Cl3N8O2·1.5H2O (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′′-tris(4-aminopyridinidium) trichloride (25)

M. p. 181 °C. – 1H NMR (200 MHz, D₂O/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. – 13C NMR (50 MHz, D₂O/D[6]-DMSO = 1 : 1): δ = 161.0, 160.4, 159.1 (2 overlapping signals), 141.4, 141.0, 115.1, 109.1, 108.6 ppm. – IR (KBr): ν = 1655, 1573, 1520, 1380, 1233, 1255, 1201, 1160, 845 cm⁻¹. – C₁₀H₁₀Cl₂N₅ · 5.5 H₂O (500.21): calcd. C 38.08, H 4.88, N 18.70; found C 37.94, H 4.90, N 18.70.

(Pyrindine-4,4-diylyl)-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′′-tris[4-(pyrrolidin-1-yl)pyridinium] trichloride (28)

M. p. 66 °C. – 1H NMR (200 MHz, D₂O): 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) ppm. – 13C NMR (50 MHz, D₂O): δ = 159.8, 159.7, 155.1, 154.5, 139.3, 139.1, 114.3, 108.4*, 49.6*, 153.9, 139.7, 139.0, 120.5 ppm. – 1H NMR (200 MHz, [D₆]-DMSO/D₂O = 1 : 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, CH₃) ppm. – IR (KBr): ν = 3416, 3055, 1560, 1571, 1464, 1386, 1248, 1176, 1088, 1051, 835 cm⁻¹. – C₁₄H₂₂Cl₂N₇ · 1.5 H₂O (393.32): calcd. C 51.53, H 5.99, N 19.99; found C 51.98, H 5.61, N 20.02.

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.

(Pyrindine-4,4-diyl)-1,1′′-bis[4-(dimethylamino)pyridinium] dichloride (31)

M. p. 313 °C. – 1H NMR (200 MHz, D₂O/D[6]-DMSO/D₂O = 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, CH₃) ppm. – 13C NMR (50 MHz, D₂O): δ = 159.2, 158.5, 157.2, 137.3, 128.7, 108.3, 100.6, 4.60 ppm. – IR (KBr): ν = 3416, 3055, 1560, 1571, 1464, 1386, 1248, 1176, 1088, 1051, 835 cm⁻¹. – C₁₄H₂₂Cl₂N₇ · 1.5 H₂O (393.32): calcd. C 51.53, H 5.99, N 19.99; found C 51.98, H 5.61, N 20.02.

(Pyrindine-4,4-diyl)-1,1′′-bis[4-(pyrrolidin-1-yl)pyridinium] dichloride (32)

M. p. 314 °C. – 1H NMR (200 MHz, D₂O/D[6]-DMSO/D₂O = 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. – 13C NMR (50 MHz, D₂O): δ = 159.7, 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. – C₁₄H₂₁Cl₂N₆ · 1 H₂O (337.18): calcd. C 47.34, H 4.54, N 23.66; found C 47.51, H 3.72, N 23.63.

(Pyrindine-4,4-diyl)-1,1′′-bis[4-(pyrrolidin-1-yl)pyridinium] dichloride (33)

M. p. 272 °C. – 1H NMR (200 MHz, D₂O/D[6]-DMSO/D₂O = 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), 2.10 – 2.15 (m, 8H, pyrrolidine) ppm. – 13C NMR (50 MHz, D₂O): 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. – C₂₃H₂₄Cl₂N₆ · 3.5 H₂O (445.80): calcd. C 53.88, H 6.37, N 17.14; found C 54.17, H 5.83, N 17.10.

(Pyrindine-2,4-diyl)-1,1′′-bis[4-(dimethylamino)pyridinium] dichloride (35)

M. p. 269 °C. – 1H NMR (200 MHz, D₂O): 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, CH₃), 3.30 (s, 6H, CH₃) ppm. – 13C NMR (50 MHz, D₂O): δ = 163.0, 158.4, 158.0, 157.9,
M. p. 332 °C. – 1H NMR (200 MHz, D2O): 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. – 13C NMR (50 MHz, D2O): δ = 163.1, 161.4, 161.3, 158.8, 154.7, 136.3, 136.0, 110.1, 109.4, 109.5 ppm. – IR (KBr): ν = 2955, 1649, 1575, 1448, 1398, 1338, 1285, 1186, 1128, 829 cm−1. – C14H14Cl2N6 (337.18): calcd. 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-trialkyl-sulfanyl-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-propoxy)-5-chloropyrimidine (43)

Pale yellow oil. – 1H NMR (200 MHz, CDCl3): δ = 5.37 (h, 3J = 6.1 Hz, 2H, CH2), 5.17 (h, 3J = 6.1 Hz, 1H, CH), 1.39 (d, 3J = 6.1 Hz, 6H, CH3); 1.38 (d, 3J = 6.1 Hz, 12H, CH3) ppm. – 13C NMR (50 MHz, CDCl3): 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 = 589 (M, 100), 348 (M–C3H7, 18), – C13H21ClN2O3 (288.77): calcd. C 53.95, H 6.87, N 9.79.

General procedure for the synthesis of the 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. – 1H NMR (200 MHz, CDCl3): δ = 5.56 (s, 1H, 5-H); 5.15 – 5.35 (m, 3H, CH2); 1.38 (d, 3J = 6.2 Hz, 6H, CH3); 1.32 (d, 3J = 6.2 Hz, 12H, CH2) ppm. – 13C NMR (50 MHz, CDCl3): 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–CH3, 100), 212 (M–C2H7, 17), 128 (M–3 C3H7, 98). – C13H21N2O3 (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 (44)

Colorless oil – 1H NMR (200 MHz, CDCl3): δ = 4.02 (h, 3J = 6.8 Hz, 2H, CH2), 3.87 (h, 3J = 6.9 Hz, 1H, CH), 1.43 (d, 3J = 6.9 Hz, 6H, CH3); 1.41 (d, 3J = 6.8 Hz, 12H, CH3) ppm. – 13C NMR (50 MHz, CDCl3): 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 CH3, 100), 227 (M–SC2H7, 41), 185 (M–SC2H7–C2H7, 31). – C13H22N2S3 (302.52): calcd. C 46.34, H 5.68, N 9.79.

General procedure for the synthesis of the 2,4,6-trialkyl-sulfanyl-pyrimidines 44 and 45

Sodium amide (1.30 g, 33 mmol), phenol (2.82 g, 0.05 mol), the 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. – 1H NMR (200 MHz, CDCl 3): δ = 6.88 – 7.35 (15, 15H) ppm. – 13C NMR (50 MHz, CDCl 3): δ = 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): ν = 3061, 1562, 1422, 1386, 1338, 1283, 1085, 1015, 815 cm⁻¹. – GC-MS: m/z = 391 (M, 100), 355 (M – Cl, 20). – C₂₅H₂₃N₂O₂ (390,80): calcd. C 67.61, 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 acetone (150 ml) and the mixture was heated under reflux for 4 hours. After cooling, the salt was distilled off in vacuo and the residue was filtered through silica gel (EtOAc/petroleum ether = 1/2). Colorless oil. – 1H NMR (200 MHz, CDCl 3): δ = 8.15 (d, 3J = 5.6 Hz, 1H, 1H, 1H, 5-H), 6.35 (d, 3J = 5.6 Hz, 1H, 1H, 1H, 5-H), 4.13 (d, 3J = 6.8 Hz, 2H, 4-OC₂), 2.15 (m, 1H, CH), 2.07 (m, 1H, CH), 1.03 (d, 3J = 6.8 Hz, 6H, 4-CH₃), 0.99 (d, 3J = 6.8 Hz, 6H, 2-CH₃) ppm. – 13C NMR (50 MHz, CDCl 3): δ = 171.4, 165.3, 158.2, 110.9, 73.8, 72.6, 27.9, 19.3, 19.2 ppm. – IR (NaCl): ν = 2961, 1585, 1422, 1386, 1328, 1283, 1085, 1015, 815 cm⁻¹. – GC-MS: m/z = 225 (MH⁺, 100), 169 (M – C₂H₅, 18), 113 (M – 2 C₂H₅), 41. – C₁₀H₁₆N₂O₂ (224.30): calcd. C 64.26, H 8.89, 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 150 ml of 2-butanol. Then, the mixture was heated under reflux for 4 hours. After cooling, the salt was distilled off in vacuo and the residue was filtered through silica gel (EtOAc/petroleum ether = 1/2). Colorless oil. – 1H NMR (200 MHz, CDCl 3): δ = 8.08 (d, 3J = 5.4 Hz, 1H, 1H, 1H, 5-H), 6.73 (d, 3J = 5.4 Hz, 1H, 1H, 5-H), 4.06 (h, 3J = 6.8 Hz, 1H, 4-CH₃), 3.93 (h, 3J = 6.9 Hz, 1H, 2-CH₃), 1.45 (d, 3J = 6.8 Hz, 6H, CH₃), 1.41 (d, 3J = 6.9 Hz, 6H, CH₃) ppm. – 13C NMR (50 MHz, CDCl 3): δ = 171.8 (C-2), 170.2 (C-2), 154.3 (C-6), 114.2 (C-5), 35.5 (CH), 34.5 (CH), 23.0 (CH₃), 22.9 (CH₂) ppm. – IR (NaCl): ν = 2964, 2927, 2866, 1518, 1504, 1513, 1213, 1051, 1056, 820 cm⁻¹. – GC-MS: m/z = 228 (MH⁺, 100). – C₁₀H₁₆N₂S₂ (228.00): calcd. C 52.59, H 7.06, N 11.34.

4,6-Di-(2-propylsulfanyl)pyrimidine (50)

M. p. -47 °C. – 1H NMR (200 MHz, CDCl 3): δ = 8.08 (d, 3J = 5.4 Hz, 1H, 1H, 1H, 5-H), 6.73 (d, 3J = 5.4 Hz, 1H, 1H, 5-H), 4.06 (h, 3J = 6.8 Hz, 1H, 4-CH₃), 3.93 (h, 3J = 6.9 Hz, 1H, 2-CH₃), 1.45 (d, 3J = 6.8 Hz, 6H, CH₃), 1.41 (d, 3J = 6.9 Hz, 6H, CH₃) ppm. – 13C NMR (50 MHz, CDCl 3): δ = 171.8 (C-2), 170.2 (C-2), 154.3 (C-6), 114.2 (C-5), 35.5 (CH), 34.5 (CH), 23.0 (CH₃), 22.9 (CH₂) ppm. – IR (NaCl): ν = 2964, 2927, 2866, 1518, 1504, 1513, 1213, 1051, 1056, 820 cm⁻¹. – GC-MS: m/z = 228 (MH⁺, 100). – C₁₀H₁₆N₂S₂ (228.00): calcd. C 52.59, H 7.06, N 11.34.

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