Synthesis of Pyridine-Thioethers via Mono- and Tricationic Pyridinium Salts

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On nucleophilic substitution with S-nucleophiles at room temperature, 1-(4-dimethylamino)-[2,3,5,6-tetrachloropyridin-4-yl]pyridinium chloride (2) yielded tetrachloro-4-sulfanylpyridines and 2,3,5-trichloro-4,6-disulfanylpyridines depending on the reaction conditions. Similarly, the tricationic (3,5-dichloropyridine-2,4,6-triyl)-1,1',1"-tris[4-(dimethylamino)pyridinium] trichloride 3 was reacted with S-nucleophiles to give the corresponding 3,5-trichloro-2,4,6-trisulfanylpyridines under mild conditions.

Key words: Nucleophilic Substitution, Thioethers, DMAP, Chloropyridines

Introduction

Pyridine and its derivatives continue to be of great interest in organic chemistry, which is reflected in an impressive number of monographs and review articles [e.g. 1 – 4]. Despite of the intense work which has been devoted to pyridines [4], a surprisingly large number of simple pyridine derivatives, especially highly substituted rings, have been unavailable to date. This contrasts to the fact that nucleophilic substitution reactions on halogenated heteroaromatics are standard reactions in organic chemistry [1 – 3]. They are known to proceed via the AE-mechanism [1 – 3], but S_N(ANRORC)-[5], EA- [6 – 8] and S_N1-mechanisms [9 – 11] are observed as well. It is also known that halogen substrates in the 2-, 3- or 4-positions of pyridine display different reactivities. Thus, 2- and 4-chloropyridine react with a large variety of nucleophiles, whereas the 3-position is inert under these reaction conditions [12 – 15] unless strong bases are used to induce EA-mechanisms [16] or metal catalysis is applied [17 – 20]. Tetrachloro-4-sulfanylpyridines, 2,3,5-trichloro-4,6-bis-sulfanylpyridines (most of which are patented [21]), and the very scarcely described class of 3,5-dichloro-2,4,6-tris-sulfanylpyridines have found interest as bactericides [22], pesticides for controlling bacteria, fungi, nematodes, insects, crustaceans, and weeds, and as host compounds [23]. In addition, they are interesting as chemical intermediates for the preparation of sulfones and sulfoxides, which are also useful as fungicides and bactericides [24], herbicides [25], biologically active compounds with fungicidal and phytotoxic activities [26], as well as insectizides and acarizides [27]. Known syntheses of pyridine-sulfanyls start from 2,3,5,6-tetrachloro-pyridine-4-thiol which can be S-methylated by dimethyl sulfate [28], S-alkylated in moderate yields [29, 30], or reacted with perfluorinated carboxylic acids under xenon difluoride catalysis [31, 32].

We found that heterarenium-substituted pyridines are suitable starting materials for the synthesis of highly substituted pyridines. In continuation of our work on betainic and oligocationic heteroaromatics [33 – 37] and their synthetic potential toward oxygen nucleophiles [38] we wish to report here a simple approach to some thioethers of chloropyridines starting from a monocationic and a tricationic pyridinium salt, respectively.

Results and Discussion

Syntheses

1-(4-Dimethylamino)-[2,3,5,6-tetrachloropyridin-4-yl]pyridinium chloride (2) and (3,5-dichloropyridine-2,4,6-triyl)-1,1',1"-tris[4-(dimethylamino)pyridinium] trichloride (3) are available in quantitative yields from pentachloropyridine 1 on reaction with 4-(dimethylamino)pyridine [36]. The salts 2 and 3 are available in quantitative yields from pentachloropyridine 1 on reaction with 4-(dimethylamino)pyridine [36].
suitable starting materials for the selective synthesis of sulfanyl-substituted pyridines, taking advantage of the leaving group tendency [36, 38] as well as of the electron-withdrawing properties of the pyridinium substituents. Thus, reaction of 2 with ethanethiol in the presence of triethylamine in acetone gave 2,3,5,6-tetrachloro-4-ethylsulfanyl-pyridine 4a in 93% yield at room temperature (Scheme). Details of the reaction conditions are summarized in Table 1. The work-up procedure is simple as possible highly polar by-products which would result from an attack at C-2 of 2 as well as unreacted starting material can easily be removed by filtration through silica gel. It is known that the formation of regioisomers is observed starting from pentachloropyridine; in the case of benzenethiolate the outcome of the substitution is dependent on solvent effects and reaction conditions [39] which is a severe limitation of this procedure. Therefore, the ethylsulfanyl derivative 4a has hitherto been prepared by a substitution / elimination sequence from pentachloropyridine 1 with dithiocarbamic acid O-ethyl ester in 55% yield [40], starting from chloro-(tetrachloro-pyridin-4-yl)-sulfane and P(OEt)3 [41], or by reaction of ethyl bromide with tetrachloro-4-mercaptopyridine [42]. 2,3,5,6-Tetrachloro-4-isopropylsulfanyl-pyridine 4b was hitherto available starting from 1 on reaction with potassium iso-propyltrithiocarbonate [43]; an additional approach is described in a patent [24]. Starting from hetarenium salt 2 this compound is formed in quantitative yield with sodium 2-propanethiolate which can be generated in situ. The corresponding tert-butyl derivative 4c is new and is formed starting from 2 by nucleophilic substitution with tert-butanethiol in acetone in the presence of triethylamine at room temperature in 64% yield. The allyl derivative 4d was prepared earlier by S-alkylation of tetrachloropyridine-4-thiol with allyl bromide after Kugelrohr distillation [44] and is formed by the method described here within 4 h at room temperature from monocation 2. Octachloro-4,4'-sulfanediyl-bis-pyridine 4e was synthesized earlier, i. a. by lithiation of tetrachloropyridine in the 4-position and subsequent treatment with SCl2 [45, 46].

Slight modifications of the reaction conditions yield the 2,3,5-trichloro-4,6-bis-sulfanylpyridines 5a–c which – to the best of our knowledge – have never been described before. They are formed in methanol

Table 1. Reaction conditions for the synthesized compounds.

<table>
<thead>
<tr>
<th>R</th>
<th>Eq.</th>
<th>Nucleophile, base</th>
<th>Solvent</th>
<th>Reaction time [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Et</td>
<td>EtSH, NEt3</td>
<td>acetone</td>
<td>18</td>
<td>93</td>
</tr>
<tr>
<td>4b</td>
<td>iPr</td>
<td>iPrSH, Na</td>
<td>–</td>
<td>2</td>
<td>99</td>
</tr>
<tr>
<td>4c</td>
<td>Bu</td>
<td>BuSH, NEt3</td>
<td>acetone</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>4d</td>
<td>allyl</td>
<td>CH2=CHCH2SH, NEt3</td>
<td>MeOH</td>
<td>4</td>
<td>76</td>
</tr>
<tr>
<td>4e</td>
<td>C5Cl4N</td>
<td>C5Cl4N-SH, NEt3</td>
<td>acetone</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>5a</td>
<td>Et</td>
<td>EtSH, Na</td>
<td>–</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>5b</td>
<td>iPr</td>
<td>iPrSH, NEt3</td>
<td>MeOH</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>5c</td>
<td>Bu</td>
<td>BuSH, NEt3</td>
<td>MeOH</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>6a</td>
<td>Et</td>
<td>exc. EtSH, NEt3</td>
<td>MeOH</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>6b</td>
<td>iPr</td>
<td>exc. iPrSH</td>
<td>MeOH</td>
<td>3</td>
<td>99</td>
</tr>
<tr>
<td>6c</td>
<td>Bu</td>
<td>exc. BuSH, NEt3</td>
<td>MeOH</td>
<td>3</td>
<td>70</td>
</tr>
</tbody>
</table>

1,2-OCB = 1,2-dichlorobenzene
(5b,c) or without solvent (5a) in moderate yields by a nucleophilic attack on the pyridinium salt 2 at C-4 and C-2 at room temperature. Using the tricationic (3,5-dichloropyridine-2,4,6-triy)-trispyridinium trichloride 3 as starting material gives the 3,5-dichloro-2,4,6-tris-sulfanylpypyridines 6a–c in fair to excellent yields. To the best of our knowledge, very few representatives of this class of compounds have been described and patented to date, among these the methyl [21, 47] and the phenyl derivative [39]. In addition, two functionalized derivatives are patented [21]. It is described that the preparation of 3,5-dichloro-2,4,6-tris-phenylsulfanyl-pyridine requires temperatures of 140 °C, a reaction time of 18 h, followed by a 12 h period of stirring with excess sodium hydroxide [39]. For the synthesis of 3,5-dichloro-2,4,6-tris-methylsulfanyl-pyridine a multi-step reaction via a pyridine-\(\text{N-oxide} \) was published [47]. The compounds 6a–c prepared as described here are formed at room temperature starting from trication 3 as indicated in Table 1.

In summary, we present an outlook dealing with the synthetic potential of the pyridinium salts 2 and 3 toward S-nucleophiles which might be of value in preparative organic and biological chemistry.

**Experimental Section**

NMR data of all compounds are presented unless they are described in the literature. The numbering C-2 to C-6 as indicated in Table 1. From aqueous ethanol.

**Mono- and Tricationic Pyridinium Salts 685**

**Synthesis of Pyridine-Thioethers**

**General procedure for the synthesis of the tetrachloro-4-allysulfanylpyridines 4a, 4b, 4c, and 4e**

A suspension of 2 (10 mmol, 3.74 g) in 75 ml of acetone was cooled to 0 °C and then treated with triethylamine (10 mmol, 1.01 g) and the corresponding thiol [ethanethiol (10 mmol, 0.62 g), 2-propanethiol (10 mmol, 0.76 g), tert-butanol (10 mmol, 0.90 g), or 2,3,5,6-tetrahydrochloropyridine-4-thiol (10 mmol, 2.51 g)]. Stirring was continued for 18 h at 0 °C (for 4a–c) or at r.t. (for 4e). The solvent was then distilled off in vacuo, the residue was filtered through silica gel (EtOAc / petroleum ether = 1/2) and recrystallized from aqueous ethanol.

**2,4,5,6-Tetrachloro-4-(ethylsulfanyl)pyridine (4a)**

M. p. 49 °C (ref. [40]: 47.5 – 48.5 °C, ref. [42]: 49 – 51 °C). NMR data are presented in ref. [40].

**2,3,5,6-Tetrachloro-4-(isopropylsulfanyl)pyridine (4b)**

M. p. 42 °C (ref. [43]: 34 – 35 °C (from hexane)). – \(\text{H NMR (200 MHz, CDCl}_3\): } \delta = 3.77 (sept, \(\text{J}\) = 6.3 Hz, 1H, CH\(_3\)), 3.18 (d, \(\text{J}\) = 6.3 Hz, 3H, CH\(_3\))

**13C NMR (50 MHz, CDCl\(_3\)): \delta = 51.4, 28.6, 146.9 (C-2, C-6), 138.0 (C-3, C-5), 55.3 (C-4, 32.0 (CH\(_2\))

**IR (KBr): \nu = 2965, 1499, 1299, 1157, 797, 671 cm\(^{-1}\). – GC-MS: m/z = 291 (M, 88), 249 (M - Cl, 100), 211 (M - C\(_3\text{H}_7\)-Cl, 23), 43 (C\(_3\text{H}_7\), 96). – C\(_8\text{H}_7\text{Cl}_4\text{N}_2\text{S} (291.03): calcd. C 33.02, H 2.42, N 4.81, S 11.02; found C 33.27, H 2.46, N 4.75, S 11.13.

**4-Allylsulfanyl-2,3,5,6-tetrachloropyridine (4c)**

M. p. 76 °C. – \(\text{H NMR (200 MHz, CDCl}_3\): } \delta = 1.44 (s, 9H, CH\(_3\)). – \(\text{13C NMR (50 MHz, CDCl}_3\): \delta = 146.9 (C-4), 146.4 (C-2, C-6), 138.0 (C-3, C-5), 55.3 (C-4, 32.0 (CH\(_2\))

\(\text{- IR (KBr): } \nu = 2965, 1499, 1299, 1157, 797, 671 \text{ cm}^{-1}. – \text{GC-MS: } m/z = 306 \text{ (M, 100).} – \text{C}_9\text{H}_8\text{Cl}_2\text{NS (305.05): calcd. C 35.44, H 2.97, N 10.51; found C 36.27, H 3.18, N 4.43, S 10.76.}

**4-tert-Butylsulfanyl-2,3,5,6-tetrachloropyridine (4d)**

M. p. 35 – 39 °C. – \(\text{13C NMR (50 MHz, CDCl}_3\): } \delta = 146.4 (C-2, C-2’, C-6, C-6’), 144.7 (C-4, C-4’), 129.6 (C-3, C-3’, C-5, C-5’)

\(\text{- IR (KBr): } \nu = 2965, 1499, 1299, 1157, 797, 671 \text{ cm}^{-1}. – \text{GC-MS: } m/z = 464 \text{ (M, 100).} – \text{C}_10\text{Cl}_8\text{N}_2\text{S (463.81): calcd. C 25.9, N 6.04; found C 26.09, N 5.87.}

**Bis-(2,3,5,6-tetrachloropyridine-4-yl)sulfane (4e)**

M. p. 35 – 39 °C. – \(\text{13C NMR (50 MHz, CDCl}_3\): } \delta = 146.4 (C-2, C-2’, C-6, C-6’), 144.7 (C-4, C-4’), 129.6 (C-3, C-3’, C-5, C-5’)

\(\text{- IR (KBr): } \nu = 2965, 1499, 1299, 1157, 797, 671 \text{ cm}^{-1}. – \text{GC-MS: } m/z = 464 \text{ (M, 100).} – \text{C}_10\text{Cl}_8\text{N}_2\text{S (463.81): calcd. C 25.9, N 6.04; found C 26.09, N 5.87.}

**4-Allylsulfanyl-2,3,5,6-tetrachloropyridine (4d)**

A suspension of 2 (10 mmol, 3.74 g) in 75 ml of methanol was cooled to 0 °C and treated with triethylamine (22 mmol, 2.8 ml) and allylmagnecapta (10 mmol, 0.74 g). After stirring for 4 h at this temperature the mixture was poured on 250 ml of ice and water, and then extracted with dichloromethane. The organic layer was evaporated to give a yellow solid which was recrystallized from aqueous ethanol.

M. p. 43 °C (ref. [44]: 42 – 43 °C). – \(\text{1H NMR (200 MHz, CDCl}_3\): } \delta = 5.75 (tt, \(\text{J}\) = 7.3 Hz, \(\text{J}\) = 10.0 Hz, 1H, CH\(_2\)),

5.10 (d, \(\text{J}\) = 1.1 Hz, 1H, =CH\(_2\)), 5.01 (d, \(\text{J}\) = 10.0 Hz, 1H, =CH\(_2\)), 3.73 (dt, \(\text{J}\) = 1.1 Hz, \(\text{J}\) = 7.3 Hz, 2H, CH\(_2\))

\(\text{- GC-MS: } m/z = 290 \text{ (MH}^+ \text{, 20), 253 (M - Cl, 100), 210 (M-Cl - C}_3\text{H}_7\), 28). – No satisfactory elemental analysis was obtained.

2,3,5-Trichloro-4,6-bis(ethylsulfanyl)pyridine (5a)

Sodium (30 mmol, 0.70 g) was dissolved in 50 ml of ethanethiol, then treated with 2 (10 mmol, 3.74 g) and stirred
for 2 h at r.t. The excess mercaptoalcohol was distilled off and the residue was chromatographed on silica gel (EtOAc / petroleum ether = 1/2) to give 5a as a yellowish oil.

1H NMR (200 MHz, [D 6]-DMSO): δ = 3.10 (s, 9H, C-4H3). – 13C NMR (50 MHz, [D 6]-DMSO): δ = 158.3 (C-2), 154.7 (C-4), 147.0 (C-6), 131.7 (C-3), 126.9 (C-5), 49.2 (C), 40.0 (C), 31.9 (CH3), 29.8 (CH3). – IR (NaCl): ν = 2964, 2925, 1503, 1456, 1365, 1290, 1157, 1079, 803 cm⁻¹. – GC-MS: m/z = 359 (MH⁺, 4), 344 (M-CH3, 91), 289 (M-2 Cl, 100), 252 (M-3 Cl), 240 (M-3 Cl-CH3, 31), 58 (C3H8, 77). – C13H18Cl3S2 (358.78): calcd. C 43.52, H 5.06, N 3.90; found C 42.28, H 4.79, N 3.55.

General procedure for the synthesis of 4,6-di(alkylsulfanyl)-2,3,5-trichloropyridines (5b and 5c)

The salt 2 (10 mmol, 3.74 g) and triethylamine (390 mmol, 4.15 ml) were dissolved in 150 ml of methanol and then treated with 2-propanethiol (30 mmol, 2.82 ml) and tert-butanol (30 mmol, 3.38 ml), respectively. The reaction mixture was then stirred for 24 h at r.t. After distilling off the solvent in vacuo at low temperatures, the residue was chromatographed on silica gel (EtOAc / petroleum ether = 1/1).

3,5-Dichloro-4,6-di(ethylsulfanyl)pyridine (6a)

M. p. 25 °C. – 1H NMR (200 MHz, [D 6]-DMSO): δ = 3.19 (q, 3J = 7.3 Hz, 2H, C-2/6-CH2), 3.04 (q, 3J = 7.3 Hz, 2H, C-4-CH2), 1.33 (t, 3J = 7.3 Hz, 3H, CH3), 1.13 (t, 3J = 7.3 Hz, 3H, CH3). – 13C NMR (50 MHz, [D 6]-DMSO): δ = 157.2 (C-4), 151.1 (C-2, C-6), 127.3 (C-3, C-5), 28.7 (C-4-CH2), 24.6 (C-2/6-CH2), 14.7 (CH3), 14.4 (2 CH3). – IR (KBr): ν = 2968, 2927, 1493, 1284, 1210, 1077 cm⁻¹. – GC-MS: m/z = 327 (M, 56), 293 (M -Cl, 100). – C11H13Cl2NS3 (328.35): calcd. C 40.24, H 4.60, N 4.27; found C 40.88, H 4.54, N 3.77.

3,5-Dichloro-4,6-di(isopropylsulfanyl)pyridine (6b)

M. p. 42 °C. – 1H NMR (200 MHz, [D 6]-DMSO): δ = 3.85 (q, 3J = 6.8 Hz, 2H, CH3), 3.80 (q, 3J = 6.8 Hz, 2H, CH3), 1.40 (t, 3J = 6.8 Hz, 6H, CH3). – 13C NMR (50 MHz, [D 6]-DMSO): δ = 163.3 (C-4), 149.0 (C-2, C-6), 127.5 (C-3, C-5), 35.3 (CH2), 22.8 (6 CH3). – IR (KBr): ν = 2965, 2927, 1681, 1504, 1457, 1293 cm⁻¹. – GC-MS: m/z = 370 (M, 100), 334 (M⁺, 41), 259 (M-Cl-C3H7S, 15). – No satisfactory elemental analysis was obtained.

2,4,6-Tris(tert-butylsulfanyl)-3,5-dichloropyridine (6c)

Yellow oil. – 1H NMR (200 MHz, [D 6]-DMSO): δ = 1.67 (s, 9H, C-4-CH3), 1.39 (s, 18H, C-2/6-CH3). – 13C NMR (50 MHz, [D 6]-DMSO): δ = 162.3 (C-4), 157.1 (C-2, C-6), 116.2 (C-3, C-5), 30.4 (3 CH3), 21.8 (9 CH3). – IR (NaCl): ν = 2930, 1737, 1677, 1458, 1387, 1245 cm⁻¹. – GC-MS: m/z = 413 (M, 12), 323 (M-C3H7S, 100), 235 (M-2 C3H7S, 47). – C17H27Cl2NS2 (412.51): calcd. C 49.50, H 6.60, N 3.40; found C 49.32, H 6.30, N 3.36.

Acknowledgement

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