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Synthesis of New Pyridines with Oligocations and Oxygen Nucleophiles

Andreas Schmidt,* Thorsten Mordhorst, and Tobias Habeck

Technische Universität Clausthal, Institut für Organische Chemie, Leibnizstrasse 6, D-38678 Clausthal-Zellerfeld, Germany

schmidt@ioc.tu-clausthal.de

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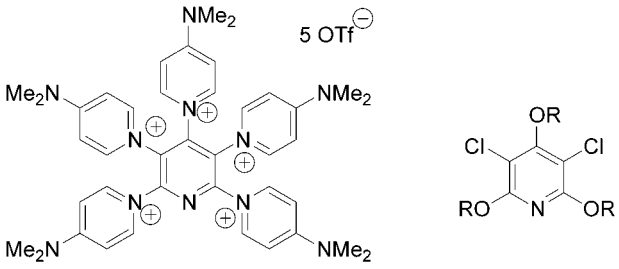
ABSTRACT

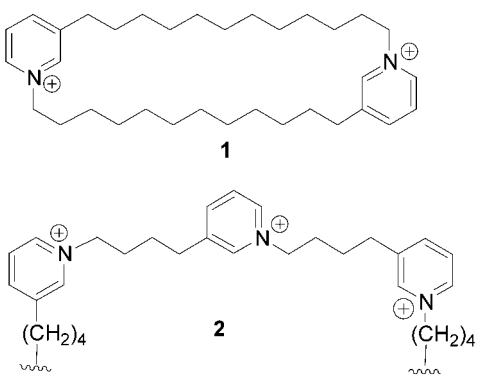


Nucleophilic substitution of 4-(dimethylamino)pyridine on pentachloropyridine yielded pentakis(pyridine-2,3,4,5,6-pentayl)pyridinium, tris-(3,5-dichloropyridine-2,4,6-triyl)pyridinium, or (tetrachloropyridin-4-yl)pyridinium depending on the reaction conditions. Nucleophilic substitution with water, hydroxides, and alcoholates resulted in new betaines and highly substituted pyridines.

Neutral as well as charged pyridine derivatives play key roles in numerous biological processes and are very interesting molecules in the field of pharmacology. The muscarinic acetylcholine receptor antagonist cyclostellettamine **1**[1] and the epidermal growth factor active polymeric pyridinium alkaloids **2**[2] (Scheme 1) are among the di- and oligocationic pyridines isolated from natural sources. In addition, highly charged systems were examined as semiconductors,[3] precursors of novel polymers[3] and stable radicals,[4] acetylcholine esterase reactivators,[5] herbicides,[6] and novel oxidizing agents.[7] However, despite intense studies directed toward the synthetic potential of heteroaromatics,[8] numerous substituted pyridines remain unknown to date.

As a continuation of our interest in charge-cumulated heteroaromatic systems,[9] we report the syntheses of 3-fold

Scheme 1



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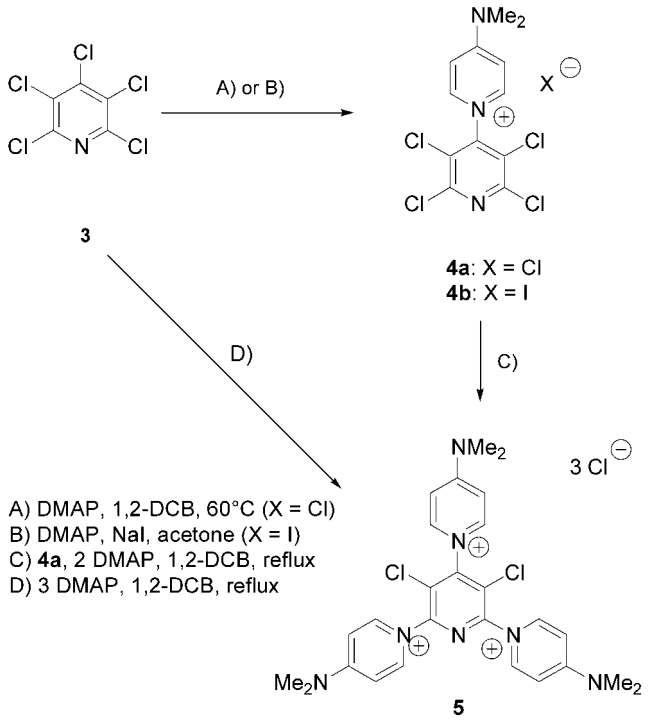
and 5-fold positively charged pyridine derivatives. Their synthetic potential for the preparation of highly substituted and hitherto unknown pyridine derivatives is examined.

Due to the limited leaving group tendency, halogenated pyridines are usually not very susceptible to more than one nucleophilic displacement by neutral nucleophiles.[10] Substitutions on pentachloropyridine with amines generally require high temperatures to produce 2-amino-substituted tetrachloropyridines.[11] High temperature (180 °C) and pressure results in 3,4-diamino-substituted trichloropyridines.[12] Peraminations of halogenopyridines are therefore not often described in the literature.[13] However, successive nucleophilic substitutions of the chlorine atoms of pentachloropyridine **3** by heteroaromatic nucleophiles cause increased activation due to the formation of strong electron-withdrawing hetarenium substituents. In contrast to chloropyrimidines,[14] the outcome of the reaction can easily be influenced by the reaction conditions which allow for the syntheses of pentacationic, tricationic, or monocationic compounds. In contrast to the reaction with aliphatic amines, heating a concentrated solution of pentachloropyridine **3** and DMAP in 1,2-dichlorobenzene (1,2-DCB) to 60 °C resulted in the formation of a slightly yellow precipitate of 1-(4-dimethylamino)-[2,3,5,6-tetrachloropyridin-4-yl]pyridinium chloride **4a** with an 87% yield (Scheme 2). Under *Finkelstein*-analogous

Scheme 2

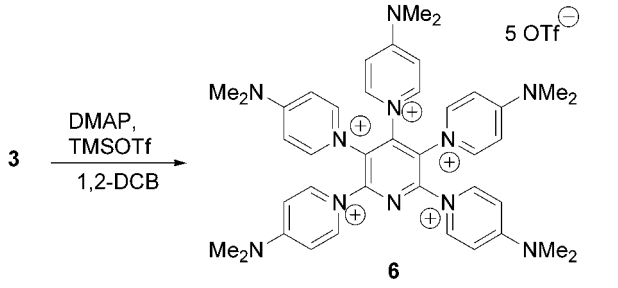


reaction conditions, refluxing a 1:1 mixture in the presence of sodium iodide in anhydrous acetone, monosubstitution at C(4) to the iodide **4b** could be observed with a 65% yield. Two resonance frequencies of heteroaromatic protons at $\delta = 7.43$ and 8.34 ppm can be seen in the ^{1}H NMR spectrum. In accordance with the symmetric structure of **4a**,**b**, the ^{13}C NMR spectra displays seven signals. The C(2)-Cl and C(3)-Cl atoms of **4b** appear at $\delta = 146.22$ and 129.31 ppm, respectively. In either case, the formation of a monocationic system is confirmed by electrospray ionization mass spectrometry (ESIMS) which gives the base peaks at $m/z = 338.0$ amu in the positive mode. The iodine derivative **4b** shows an additional peak at $m/z = 802.8$ amu at fragmentor voltages between 0 and 10 V which obviously corresponds to a monocationic π-sandwich complex between two molecules of $\mathbf{4}^+$ and one iodine anion.

Heating the same solution for 40 min at reflux temperature in an inert atmosphere resulted in the almost quantitative formation of a yellow precipitate of 1,1′,1″-tris[4-(dimethylamino)-(3,5-dichloropyridine-2,4,6-triyl)pyridinium] trichloride **5**, which can be stored under nitrogen. The ^{1}H NMR spectrum, the peaks for the β-protons appear at 8.83 and 8.66 ppm and the α-protons at 7.49 and 7.34 ppm in 2:1 and 1:2 ratios, respectively.

We then focused our interest on the synthetic potential of this new tricationic system. More vigorous reaction conditions converted pentachloropyridine **3** or trication **5** and DMAP into a 5-fold positively charged species. Thus, treatment of **3** with 4-(dimethylamino)pyridine in 1,2-dichlorobenzene in the presence of 5−6 equiv of trifluoromethylsulfonic acid trimethylsilyl ester (TMSOTf) at reflux temperature resulted in the formation of a slightly yellow precipitate of 1,1′,1″,1‴,1⁗-pentakis[4-(dimethylamino)-(pyridine-2,3,4,5,6-pentayl)pyridinium] pentakis(trifluoromethylsulfonate) **6** in a yield of 31%, which proved stable in air (Scheme 3). The leaving group is trapped as volatile

Scheme 3



TMSCl when this method is applied. Molecular mass as well as the 5-fold positive charge is unambiguously confirmed

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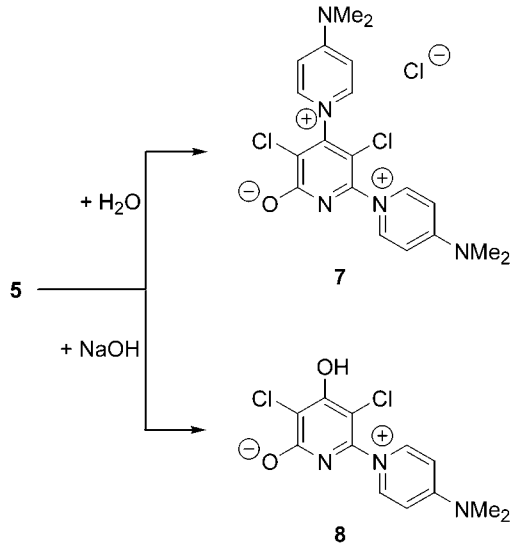
by electrospray ionization mass spectrometry (ESIMS). Spraying an acetonitrile solution at 0 V fragmentor voltage results in peaks at m/z = 1280.4 [$\mathbf{6}^{5+}$ − OTf^-], 565.7 [$\mathbf{6}^{5+}$ − 2OTf^-], and 327.5 [$\mathbf{6}^{5+}$ − 3 OTf^-]. ^{1}H NMR spectroscopy in DMSO-d_6 resulted in the detection of resonance frequencies of three distinct types of pyridinium β-hydrogen atoms at δ = 8.23, 8.05, and 7.87 ppm, the ratio of which is 2:2:1. The β-hydrogen atoms form a multiplet at 7.23 ppm.

Water converted the trication **5** under loss of two positive charges into the tripolar system **7** which is slightly yellow in color (75% yield). This reaction obviously involves nucleophilic attack at C-2 of the central pyridine moiety, extrusion of one DMAP molecule, and subsequent deprotonation of the resulting hydroxy group (Scheme 4).

Scheme 4



Two sets of 4-(dimethylamino)pyridinium rings at δ = 8.65/8.49 ppm (β positions) and 7.44/7.32 ppm (α positions) in a 1:1 ratio and no deuterium-exchangeable protons such as NH (pyridone) or OH groups (pyridol) are observed in the ^{1}H NMR spectrum. No dicationic species can be detected by ESI mass spectrometry. The ^{13}C NMR spectrum suggests the formation of a nonsymmetric molecule since 13 signals are detected. The central pyridine ring gives resonance frequencies at 126.4, 131.1, 146.6, 147.0, and 191.6 ppm. The last-mentioned signal is due to the C(2)-O group.

After heating at reflux temperature, a diluted aqueous solution of sodium hydroxide induced the nucleophilic displacement of two pyridinium rings of the trication **5** to yield the 2-pyridinium-substituted 4,6-dihydroxypyridine **8** as a cross-conjugated mesomeric betaine.[15] The protonation site cannot unambiguously be determined by NMR spectroscopy.

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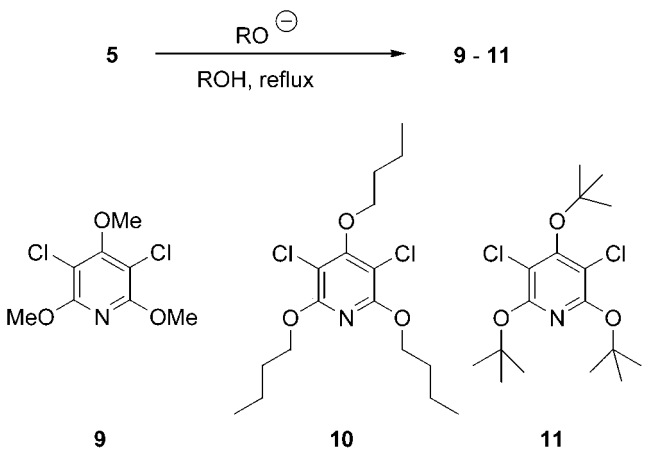
We then directed our attention to alcohols as potential nucleophiles. It is known that 2- or 4-substitution on pentachloropyridine proceeds at high temperatures to give monosubstituted tetrachloropyridines[16] or 2,4-disubstituted trichloropyridines.[17] The methoxy derivative **9** was hitherto available through a two-step procedure starting from 2,4,6-trichloropyridine which reacts with sodium methoxide (sealed tube, 135 °C) followed by chlorination of the resulting 2,4,6-trimethoxypyridine with phosphorus pentachloride,[18] or alternatively by substituting pentachloropyridine **3** with methanolate in DMF[19] with a low yield. Treatment of the trication **5** with sodium alkoxides in the corresponding alcohols at reflux temperature over a period of 2 h, however, resulted in the smooth formation of 2,4,6-trialkoxy-substituted pyridines. Thus, methanolate in methanol, *n*-butanolate in butanol, and *tert*-butanolate in *tert*-butanol, respectively, gave the 3,5-dichloro-2,4,6-trialkoxypyridines **9**−**11** in good yields (Scheme 5). In either case, two distinct types of alkoxy

Scheme 5



substituents in a 1:2 ratio can be observed in the ^{1}H NMR spectrum.

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Supporting Information Available: Spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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