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Preparation of 4-Alkoxy-1-hydroxypyridine-2-thiones*

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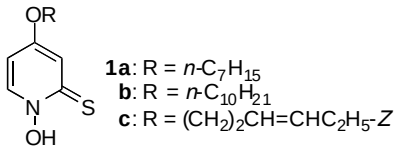
Reactions of 2-chloro-4-fluoropyridine (**8**), 2-chloro-4-nitropyridine (**9**), and their corresponding *N*-oxides **7** and **3** with the *n*-heptanolate anion were investigated in three solvents. The desired 2-chloro-4-heptyloxypyridine-*N*-oxide (**4a**) was obtained most efficiently from **3** in DMSO. A reaction of **4a** with AcSNa followed by deacetylation with MeONa gave the sodium salt of 4-heptyloxy-1-hydroxypyridine-2-thione (**1a**), which was isolated as the adamantane-1-carboxylate *O*-ester **2a**. Similarly, the 4-decyloxy and 4-((*Z*)-hex-3-enyloxy) derivatives **2b** and **2c** were prepared from **3**.

Key words: heterocycles, pyridine-2-thione, aromatic nucleophilic substitution

1-Hydroxypyridine-2-thione has been extensively used as a reagent in synthetic chemistry [1], an active component of medicinal and cosmetic products [2], and as a ligand for metal complexes [3–5]. Surprisingly, there has been little effort to investigate derivatives of this heterocycle and to optimize its properties for applications. The few known substituted 1-hydroxypyridine-2-thiones include 4-propyl [6], 4-fluoroalkyl [5], mercapto [7], 4-methoxycarbonyl [8], 3-ethoxy [9] and several methyl [9–11] and dimethyl [10] derivatives. Many of these compounds are described in the patent literature [12] and only a handful main-stream publications have been dedicated to the chemistry of the substituted 1-hydroxypyridine-2-thione. Our interest in this class of compounds prompted us to develop synthetic access to virtually unknown 4-alkoxy-1-hydroxypyridine-2-thiones such as **1** [13].

In this paper we report systematic investigation and preparation of three 4-alkoxy derivatives of 1-hydroxypyridine-thione **1**, which were isolated and characterized as adamantane-1-carboxylic acid *O*-esters **2**.

Structure **1**



1a: R = *n*-C_7H_{15}
b: R = *n*-$C_{10}H_{21}$
c: R = $(CH_2)_2CH{=}CHC_2H_5$-*Z*

* Dedicated to Prof. Jacek Młochowski on the occasion of his 70th birthday.
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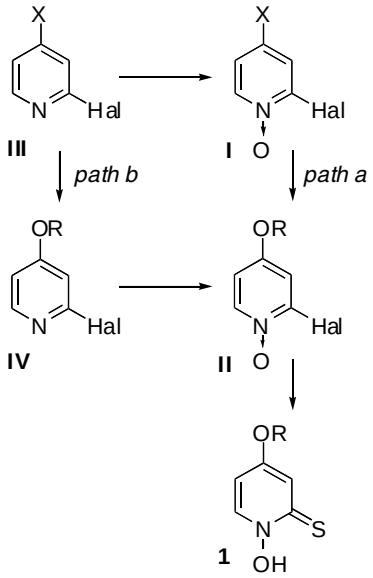
RESULTS AND DISCUSSION

Synthesis of 1-hydroxypyridine-2-thiones typically involves a reaction of appropriate 2-halopyridine-*N*-oxide with a hydrosulfanylating reagent such as NaHS [5,6,9,14], thiourea [8], or thioacetamide [7]. Therefore, the preparation of 4-substituted thiones **1** can be envisioned as sequential substitution of group X with an alkoxy group followed by replacement of the halogen with hydrosulfanyl as shown in Scheme 1. The use of *N*-oxide **I** as the common starting material in *path a* allows for the preparation of **1** in two steps through oxide **II**, and eliminates the occasionally troubling *N*-oxidation step in *path b* (**IV**→ **II**). A successful synthesis of **1**, according to Scheme 1, requires higher mobility of X relative to the halogen in nucleophilic aromatic substitution [15] in both precursors, **I** in *path a* and **III** in *path b*.

Scheme 1

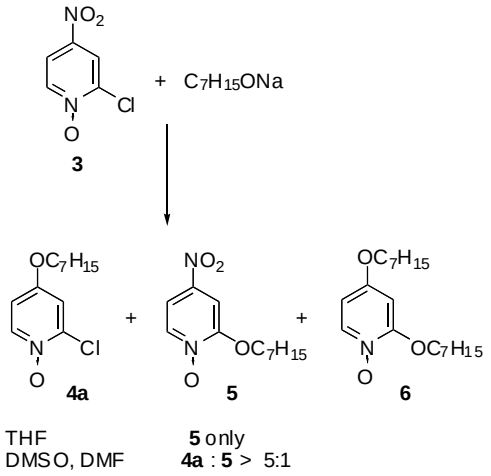


A search for commercially available reagents of type **I** led to 2-chloro-4-nitropyridine-*N*-oxide (**3**). To establish regioselectivity of nucleophilic substitution in **3**, we investigated its reaction with sodium *n*-heptanolate in three solvents: THF, DMF, and DMSO (Scheme 2). Analysis of the reaction products obtained from **3** and 1 equivalent of the *n*-heptanolate in THF revealed that the desired 4-heptyloxy derivative **4a** was completely absent and the 2-heptyloxy derivative **5** was the sole product isolated in 44% yield. This yield was increased to 62% when 2 equivalents of the nucleophile were used and the reaction was conducted for 90 min at ambient temperature. When left overnight, the 2,4-diheptyloxypyridine-*N*-oxide (**6**) was the main product as evident from NMR and MS analysis.

Reactions of **3** with 1 equivalent of the *n*-heptanolate conducted in DMF and DMSO gave the 4-heptyloxy derivative **4a** as the main product. The amounts of **5** varied somewhat from run to run but they were always less than 20% of **4a**. Also reactions run in DMSO appeared to be cleaner than those performed in DMF. In each reaction, however, there was up to 50% of unreacted heptanol recovered, despite the use of rigorously dried solvents, and no starting **3** was observed in the worked-up reaction mixture. The use of 20% excess NaH did not improve the conversion of the alcohol. The disubstituted product **6** was generally absent or appeared in trace amounts based on the NMR spectra of the crude mixtures. On the basis of these results, preparative scale reactions of **3** were conducted in DMSO, and **4a** was being isolated in a consistent yield of about 30–35%.

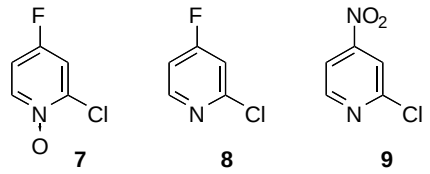
The selectivity for the 2 position observed in the heptyloxylation of **3** in THF is consistent with scant literature reports. Thus, it was reported that a reaction of **3** with either allyloxide or benzyloxide anion in THF gave the corresponding 2-substituted derivatives as sole products isolated in 44% and 79% yield, respectively [16]. In contrast, reaction of **3** with MeONa in methanol gave the 4-methoxy-2-chloro derivative in 70% yield [16,17].

Scheme 2



In order to increase the efficiency of the alkoxylation reaction, we briefly investigated 2-chloro-4-fluoropyridine-*N*-oxide (**7**), the fluoro analog of **3**, which was prepared by oxidation of the available 2-chloro-4-fluoropyridine (**8**). We also investigated the preparation of **4a** *via path b* using pyridines **8** and **9** (compounds of type **III** in Scheme 1).

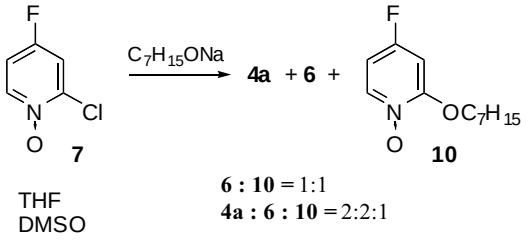
Structures **7–9**



7 **8** **9**

Results showed that reactions of *N*-oxide **7** with of sodium *n*-heptanolate proceed with lower selectivity than those of **3** under similar conditions. In both solvents, THF and DMSO, reactions of **7** with 1 equivalent of the nucleophile gave significant amounts of 2,4-diheptyloxy derivative **6** (Scheme 3). In THF a reaction of **7** gave the 2-substituted derivative **10** and 2,4-diheptyloxy **6** in approximately equal amounts, in spite of the fact that only about half of *n*-heptanol was consumed. In DMSO however, 4-heptyloxy derivative **4a** was formed in twice the amount of **10** and was equal to the amounts of 2,4-diheptyloxy derivative **6**. These results indicate that the 2-Cl is only somewhat more reactive than 4-F and significantly more reactive than 4-NO_2 in THF. In DMSO the order is reversed and 4-NO_2 appears to be most reactive followed by 4-F and 2-Cl.

Scheme 3



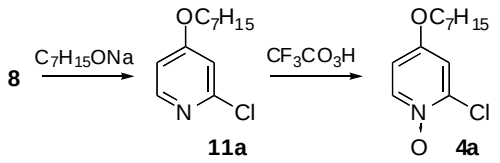
7 **10**

6 : 10 = 1:1
4a : 6 : 10 = 2:2:1

In contrast to *N*-oxides, substrates **8** and **9** smoothly reacted with the *n*-heptanolate in both DMSO and THF giving the 4-heptyloxy derivative **11a** as the sole product (Scheme 4). Thus, product **11a** was conveniently isolated in 63% yield from the reaction of **8** with *n*-heptanolate in THF. These results are consistent with literature reports showing that **9** smoothly reacts with alcoholates in a variety of solvents giving the corresponding 4-alkoxy derivatives in moderate to very good yields [16, 18–22].

Oxidation of **11a** to **4a** was accomplished using CF_3CO_3H in CH_2Cl_2. The reaction required 2 days for completion and the product was isolated in 40% yield (Scheme 4). Attempted oxidation of **11a** with H_2O_2 in the presence of a Re catalyst [23] did not work, and after 2 days no product was detected and most starting material was recovered.

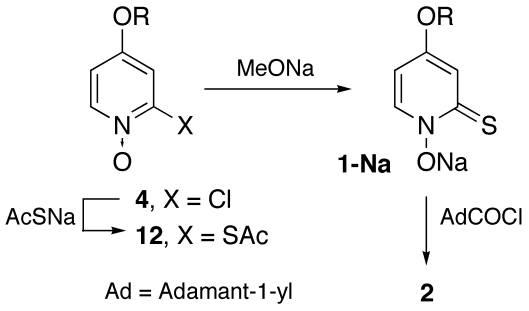
Scheme 4



The chloro derivative **4a** was further transformed to the thione **1a** as shown in Scheme 5. The *N*-oxide **4a** was reacted with AcSNa generated *in situ* in dry MeCN to give thioacetate **12a**, which subsequently was reacted with 1 eq of MeONa in dry MeOH. Evaporation of the solution gave the sodium salt of the thione **1a-Na** with the purity >90%. The free thione **1a** was liberated with dil HCl and analyzed by NMR and MS techniques. Both, the thioacetate and the thione are oils that are sensitive to silica gel and therefore could not be rigorously purified. For the purpose of analysis, the sodium salt **1a-Na** was treated with adamantane-1-carbonyl chloride to give the crystalline ester **2a**.

The same method was used to prepare the 4-decyloxy and 4-(*Z*-hex-3-enyloxy) derivatives, **2b** and **2c**, respectively from the corresponding *N*-oxides **4b** and **4c**. In all three cases the overall yield for the preparation of the *O*-esters was about 50–60% based on **4**. The required chlorides **4b** and **4c** were obtained from **3** in DMSO as described for **4a**.

Scheme 5



CONCLUSIONS

The preparation of 4-alkoxypyridine-2-thiones (**1**) was accomplished in three steps and a reproducible overall yield of about 30% from the common precursor **3**. The modification of the hydrosulfanylation step by using AcSNa/MeONa allows for the efficient and convenient preparation of the thione sodium salt **1-Na** in purity sufficient for the *O*-acylation step.

In *path b* the alkoxylation step proceeds more easily but the required *N*-oxidation step is only moderately efficient and it may interfere with the alkene functionality present in the substituent. A comparison of results for pyridines **8** and **9** with those for their respective *N*-oxides **7** and **3** demonstrated that oxidation of the nitrogen atom significantly lowers the mobility of the substitutent in the 4 position (NO_2 and F). In consequence, alkoxylation of pyridines **8** and **9** is highly selective for the 4 position, while the same reaction of *N*-oxides **7** and **3** occurs at 2 position in THF. In DMSO a mixture of the two products is obtained with the preference for the 4 substitution.

EXPERIMENTAL

^{1}H NMR spectra were obtained at 300 MHz field in $CDCl_3$ and referenced to the solvent. Melting points were taken in an open capillary.

4-Alkoxy-1-hydroxypyridine-2-thione sodium salts (1-Na). General procedure. To the solution of crude 2-thioacetoxy-4-alkoxypyridyne-*N*-oxide (**12**, 1 mmol) in dry methanol (2 mL), the methanol solution of sodium methanolate (1 mmol) was added. The reaction mixture was stirred for 0.5 h and solvent was evaporated. The resulting solid (100%) of crude **1-Na** was used for the preparation of esters **2**. Samples of 4-alkoxy-1-hydroxypyridine-2-thiones (**1**) were obtained by treatment of **1-Na** with dil HCl and extracting the product to CH_2Cl_2. Evaporation of the solvent left thione **1** as a yellowish viscous oil, which was >95% pure, based on NMR analysis.

4-Heptyloxy-1-hydroxypyridine-2-thione (1a). ^{1}H NMR δ 0.89 (t, J = 6.6 Hz, 3H), 1.20–1.47 (m, 8H), 1.78 (quin, J = 6.9 Hz, 2H), 3.97 (t, J = 6.5 Hz, 2H), 6.37 (dd, J_1 = 7.5 Hz, J_2 = 3.1 Hz, 1H), 7.10 (d, J = 3.1 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H). HRMS, calcd for $C_{12}H_{20}NO_2S$: *m/z* 242.1215; found: *m/z* 242.1197.

4-Decyloxy-1-hydroxypyridine-2-thione (1b). ^{1}H NMR δ 0.88 (t, J = 6.6 Hz, 3H), 1.22–1.47 (m, 14H), 1.77 (quin, J = 6.9 Hz, 2H), 3.97 (t, J = 6.5 Hz, 2H), 6.37 (dd, J_1 = 7.5 Hz, J_2 = 3.1 Hz, 1H), 7.10 (d, J = 3.1 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H); FAB MS, *m/z* 284 (MH^+, 75), 268 (34), 144 (100). HRMS, calcd for $C_{15}H_{26}NO_2S$: *m/z* 284.1684; found: *m/z* 284.1689.

4-((*Z*)-Hex-3-enyloxy)-1-hydroxypyridine-2-thione (1c). ^{1}H NMR δ 0.99 (t, J = 7.5 Hz, 3H), 2.07 (quin, J = 7.1 Hz, 2H), 2.53 (q, J = 6.7 Hz, 2H), 3.97 (t, J = 6.8 Hz, 2H), 5.35 (dtt, J_1 = 10.8 Hz, J_2 = 7.2 Hz, J_3 = 1.6 Hz, 1H), 5.56 (dtt, J_1 = 10.8 Hz, J_2 = 7.3 Hz, J_3 = 1.5 Hz, 1H), 6.37 (dd, J_1 = 7.5 Hz, J_2 = 3.1 Hz, 1H), 7.10 (d, J = 3.1 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H); FAB MS, *m/z* 226 (MH^+, 100), 207 (65), 147 (78). HRMS, calcd for $C_{11}H_{16}NO_2S$: *m/z* 226.0902; found: *m/z* 226.0903.

Adamantane-1-carboxylate esters 2. General procedure. Adamantane-1-carbonyl chloride (1.0 mmol) was added to the suspension of sodium salt **1-Na** (1.0 mmol) in dry CH_2Cl_2 (2 mL) and the reaction mixture was stirred for 2–14 h. It was passed through a silica gel plug and the product was eluted with CH_2Cl_2. The solvent was evaporated and the solid residue was recrystallized from MeCN/AcOEt to give white crystalline product.

Ester 2a. Yield 50%: m.p. 111–112°C; ^{1}H NMR δ 0.89 (t, J = 6.6 Hz, 3H), 1.23–1.46 (m, 8H), 1.71–1.82 (m, 8H), 2.06–2.13 (m, 3H), 2.14–2.19 (m, 6H), 3.96 (t, J = 6.5 Hz, 2H), 6.26 (dd, J_1 = 7.7 Hz, J_2 = 3.2 Hz, 1H), 7.11 (d, J = 3.1 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H). Anal. Calcd for $C_{23}H_{33}NO_3S$: C, 68.45; H, 8.24. Found: C, 68.17; H, 8.20.

Ester 2b. Yield 62%: ^{1}H NMR δ 0.88 (t, J = 6.5 Hz, 3H), 1.20–1.45 (m, 14H), 1.65–1.82 (m, 8H), 2.06–1.82 (m, 3H), 2.14–2.19 (m, 6H), 3.96 (t, J = 6.5 Hz, 2H), 6.26 (dd, J_1 = 7.7 Hz, J_2 = 3.1 Hz, 1H), 7.10 (d, J = 3.1 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H).

Ester 2c. Yield 62%: ^{1}H NMR δ 0.98 (t, J = 7.5 Hz, 3H), 1.75–1.79 (m, 6H), 2.02–2.12 (m, 5H), 2.17 (br d, J = 2.8 Hz, 6H), 2.51 (brq, J = 6.8 Hz, 2H), 3.96 (t, J = 6.7 Hz, 2H), 5.33 (dtt, J_1 = 10.8 Hz, J_2 = 7.2 Hz, J_3 = 1.5 Hz, 1H), 5.55 (dtt, J_1 = 10.8 Hz, J_2 = 7.3 Hz, J_3 = 1.6 Hz, 1H), 6.26 (dd, J_1 = 7.7 Hz, J_2 = 3.2 Hz, 1H), 7.11 (d, J = 3.2 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H).

2-Chloro-4-nitropyridine-*N*-oxide (3). ^{1}H NMR δ 8.05 (dd, J_1 = 7.2 Hz, J_2 = 3.0 Hz, 1H), 8.38 (d, J = 3.0 Hz, 1H), 8.40 (d, J = 7.3 Hz, 1H).

4-Alkyloxy-2-chloropyridine-*N*-oxides 4. **General procedure**. Alcohol (1 mmol) was added to the suspension of NaH (1.2 mmol) in dry DMSO (5 mL) and the reaction mixture was stirred for 2 h under N_2 atmosphere. Then a solution of 2-chloro-4-nitropyridine-*N*-oxide (**3**, 175 mg, 1 mmol) in dry DMSO (2 mL) was added. The reaction mixture was stirred for 24 h at rt, poured into water, extracted (AcOEt, 3×10 mL), dried (Na_2SO_4), solvents were evaporated, and the remaining of DMSO was removed under vacuum. The crude product was purified by column chromatography (acetone/MeOH, 10:1) to give **4** (>95% purity by NMR) as a yellowish oil.

2-Chloro-4-heptyloxypyridine-*N*-oxide (4a). Yield 33%: ^{1}H NMR δ 0.89 (t, J = 6.8 Hz, 3H), 1.25–1.50 (m, 8H), 1.80 (quin, J = 6.9 Hz, 2H), 3.98 (t, J = 6.5 Hz, 2H), 6.76 (dd, J_1 = 7.2 Hz, J_2 = 3.3 Hz, 1H), 6.99 (d, J = 3.3 Hz, 1H), 8.23 (d, J = 7.3 Hz, 1H); FAB MS, *m/z* 244 (MH^+, 100), 146 (77). HRMS, calcd for $C_{12}H_{19}ClNO_2$: *m/z* 244.1104; found: *m/z* 244.1092.

2-Chloro-4-decyloxypyridine-*N*-oxide (4b). Yield 35%: ^{1}H NMR δ 0.88 (t, J = 6.6 Hz, 3H), 1.20–1.49 (m, 14H), 1.79 (quin, J = 6.9 Hz, 2H), 3.98 (t, J = 6.5 Hz, 2H), 6.76 (dd, J_1 = 7.3 Hz, J_2 = 3.3 Hz, 1H), 6.99 (d, J = 3.3 Hz, 1H), 8.23 (d, J= 7.3 Hz, 1H); FAB MS, *m/z* 286 (MH^+, 80), 252 (58), 146 (71), 112 (100). HRMS, calcd for $C_{15}H_{25}ClNO_2$: *m/z* 286.1574; found: *m/z* 286.1564.

2-Chloro-4-((*Z*)-hex-3-enyloxy)pyridine-*N*-oxide (4c). Yield 30%: ^{1}H NMR δ 0.98 (t, J = 7.5 Hz, 3H), 2.09 (quin, J = 7.3 Hz, 2H), 2.54 (q, J = 6.9 Hz, 2H), 3.98 (t, J = 6.8 Hz, 2H), 5.36 (dtt, J_1 = 10.7 Hz, J_2 = 7.3 Hz, J_3 = 1.5 Hz, 1H), 5.56 (dtt, J_1 = 10.8 Hz, J_2 = 7.3 Hz, J_3 = 1.6 Hz, 1H), 6.76 (dd, J_1 = 7.3 Hz, J_2 = 3.3 Hz, 1H), 7.00 (d, J = 3.3 Hz, 1H), 8.23 (d, J = 7.3 Hz, 1H); FAB MS, *m/z* 228 (MH^+, 100), 194 (78), 146 (77). HRMS, calcd for $C_{11}H_{15}ClNO_2$: *m/z* 228.0791; found: *m/z* 228.0778.

2-Heptyloxy-4-nitropyridine-*N*-oxide (5). *n*-Heptanol (3.25 g, 28 mmol) was added to the suspension of NaH (800 mg, 60% in oil, 20 mmol) in dry THF (100 mL) and the reaction mixture was stirred for 1 h under N_2 atmosphere. The solution of 2-chloro-4-nitropyridine-*N*-oxide (**3**, 2.44 g, 14 mmol) in dry THF (10 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h, poured into NH_4Cl, extracted (CH_2Cl_2, 3×5 mL), dried (Na_2SO_4) and solvents were evaporated. The solid residue was purified by crystallization (*i*-octane) to give 2.10 g (62% yield) of **5** as a yellow crystalline solid: m.p. 82–83°C; ^{1}H NMR δ 0.89 (t, J = 6.5 Hz, 3H), 1.26–1.44 (m, 6H), 1.45–1.58 (m, 2H), 1.98 (quin, J = 7.2 Hz, 2H), 4.31 (t, J = 6.7 Hz, 2H), 7.71 (d, J = 2.8 Hz, 1H), 7.77 (dd, J_1 = 7.1 Hz, J_2 = 2.4 Hz, 1H), 8.34 (d, J = 7.1 Hz, 1H). Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.87; H, 10.97; N, 10.97.

2,4-Diheptyloxypyridine-*N*-oxide (6). A reaction of **3** with 2 eq of *n*-$C_7H_{15}ONa$ conducted in THF over 24 h at room temperature gave **6** as the sole product: ^{1}H NMR δ 0.85–0.92 (m, 6H), 1.25–1.55 (m, 16H), 1.79 (quin, J= 6.8 Hz, 2H), 1.94 (quin, J = 7.1 Hz, 2H), 3.97 (t, J= 6.5 Hz, 2H), 4.19 (t, J = 7.0 Hz, 2H), 6.37 (d, J = 3.0 Hz, 1H), 6.44 (dd, J_1 = 7.3 Hz, J_2 = 2.9 Hz, 1H), 8.15 (d, J = 7.3 Hz, 1H); FAB MS, *m/z* 324 (MH^+, 100), 226 (61). HRMS, calcd for $C_{19}H_{34}NO_3$: *m/z* 324.2539; found: *m/z* 324.2536.

2-Chloro-4-fluoropyridine-*N*-oxide (7). A solution of 2-chloro-4-fluoropyridine (**8**, 0.50 g, 3.8 mmol) and mCPBA (3.0 g, ~50% pure) in dry CH_2Cl_2 (10 mL) was stirred overnight at ambient temperature. It was washed with 10% NaOH (20 mL), water (20 mL), extracted with CH_2Cl_2 (3×10 mL), dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2 followed by acetone) to afford 330 mg (58% yield) of *N*-oxide **7** as a yellowish oil: ^{1}H NMR δ 6.99–7.08 (m, 1H), 7.77 (dd, J_1 = 6.0 Hz, J_2 = 3.1 Hz, 1H), 8.34 (t, J = 6.3 Hz, 1H); FAB MS, *m/z* 148 (MH^+, 100), 130 (44), 114 (44). HRMS, calcd for C_5H_4ClFNO: *m/z* 147.9965; found: *m/z* 147.9967.

Reaction of 2-chloro-4-fluoropyridine-*N*-oxide (7) with *n*-$C_7H_{15}ONa$. The reaction was conducted in THF in the same way as described for the preparation of **4a** in DMSO. The reaction mixture was worked up and the NMR analysis of the crude product showed two sets of signals in approximate ratio of 1:1 attributed to **6** and **4-fluoro-2-heptyloxypyridine-*N*-oxide (10)**: ^{1}H NMR (selected signals) δ 4.21 (t, J = 7.0 Hz, 2H), 6.63–6.71 (m, 2H), 8.25 (t, J = 6.6 Hz, 1H).

2-Chloro-4-fluoropyridine (8). ^{1}H NMR (400 MHz) δ 7.00 (td, J_1 = 6.7 Hz, J_2 = 2.0 Hz, 1H), 7.10 (dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, 1H), 8.38 (dd, J_1 = 8.3 Hz, J_2 = 5.7 Hz, 1H).

2-Chloro-4-heptyloxypyridine (11). *n*-Heptanol (88 mg, 0.76 mmol) was added to the suspension of NaH (37 mg, 60% in oil, 0.9 mmol) in dry THF (2 mL) and the reaction mixture was stirred for 1 h under N_2 atmosphere. 2-Chloro-4-fluoropyridine (**8**, 100 mg, 0.76 mmol) in dry THF (1 mL) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was poured into water, extracted with CH_2Cl_2 (3×5 mL), dried (Na_2SO_4), solvents were evaporated, and the remaining heptanol was

removed under vacuum. The crude oily product was purified by column chromatography (SiO_2, CH_2Cl_2) to give 123 mg (62% yield) of **11** as a colorless oil: ^{1}H NMR δ 0.89 (t, *J*= 6.7 Hz, 3H), 1.22–1.50 (m, 8H), 1.79 (quin, *J* = 7.0 Hz, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 6.72 (dd, J_1 = 5.8 Hz, J_2 = 2.1 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 8.16 (d, *J* = 5.8 Hz, 1H). Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97. Found: C, 63.73; H, 8.03.

4-Alkoxy-2-thioacetoxypyridine-*N*-oxides (12). General procedure. Thioacetic acid (76 mg, 1.0 mmol) was added to the suspension of NaH (1.0 mmol) in dry MeCN (2 mL). After 20 min the solution was added to 4-alkyloxy-2-chloropyridine-*N*-oxide (**4**, 1 mmol) in MeCN. The reaction mixture was stirred for 0.5 h, poured into 2% HCl, extracted with CH_2Cl_2 (3×10 mL), dried (Na_2SO_4) and the solvent was removed. The oily residue (quantitative yield) was used without purification for the preparation of **1-Na**. Attempted separation of **12** on a silica gel column resulted in decomposition of the compound.

4-Heptyloxy-2-thioacetoxypyridine-*N*-oxide (12a). ^{1}H NMR δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.20–1.45 (m, 8H), 1.77 (quin, *J*= 6.9 Hz, 2H), 2.44 (s, 3H), 3.97 (t, *J* = 6.5 Hz, 2H), 6.28 (dd, J_1 = 7.7 Hz, J_2 = 3.2 Hz, 1H), 7.11 (d, *J* = 3.2 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H). HRMS, calcd for $C_{14}H_{22}NO_3S$: *m/z* 284.1320; found: *m/z* 284.1323.

4-Decyloxy-2-thioacetoxypyridine-*N*-oxide (12b). ^{1}H NMR δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.25–1.48 (m, 14H), 1.77 (quin, *J* = 7.0 Hz, 2H), 2.43 (s, 3H), 3.97 (t, *J* = 6.5 Hz, 2H), 6.28 (dd, J_1 = 7.7 Hz, J_2 = 3.2 Hz, 1H), 7.11 (d, *J* = 3.2 Hz, 1H), 7.43 (d, *J*= 7.7 Hz, 1H).

4-((*Z*)-Hex-3-enyloxy)-2-thioacetoxypyridine-*N*-oxide (12c). ^{1}H NMR δ 0.98 (t, *J* = 7.5 Hz, 3H), 2.07 (quin, *J* = 7.4 Hz, 2H), 2.43 (s, 3H), 2.52 (q, *J*= 6.6 Hz, 2H), 3.97 (t, *J* = 6.7 Hz, 2H), 5.28–5.41 (m, 1H), 5.49–5.62 (m, 1H), 6.28 (dd, J_1 = 7.7 Hz, J_2 = 3.2 Hz, 1H), 7.11 (d, *J* = 3.2 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H); FAB MS, *m/z* 268 (MH^+, 38), 226 (57) 147 (100). HRMS, calcd for $C_{13}H_{18}NO_3S$: *m/z* 268.1007; found: *m/z* 268.1016.

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