IR (neat) 1764 (cyclobutanone C=O) and 1738 (acetate C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34-6.97 (m, 4 H, Ar-H), 4.90 (d, 1 H, J = 6 Hz, C*H*OAc), 2.82 (AB q, 2 H, J = 17 Hz, benzylic CH_2), 2.52 (s, 1 H, benzylic CH), 2.05 (m, 4 H, $COCH_3$ and $CHCH_3$), 1.16 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 0.73 (d, 3 H, J = 8 Hz, $CHCH_3$); MS m/e (rel intensity) 312 (M^+, 3), 270 (42), 225 (13), 209 (32), 169 (70), 157 (100), 142 (35), 128 (15), 113 (18). Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.84; H, 7.85.

Nitrogen laser irradiation of 0.01 M solutions of enone **9** in acetonitrile at temperatures ranging from -40 to +56 °C gave **9CB** as the only product detectable by GC. Laser photolysis of KBr pellets containing crystalline **9** gave IR spectra identical with that of **9CB**; similar irradiation of polycrystalline **9** gave a single product identical with that formed in solution as shown by GC co-injection analysis.

Interconversion of Photoproducts 9CB and 8HA. A stirred solution of cyclobutanone-acetate **9CB** (20 mg, 0.06 mmol) in 2 mL of methanol was treated with 1 mL of a 2% aqueous solution of sodium hydroxide for 3 h at room temperature. The reaction mixture was extracted with ether (2 × 3 mL), and the combined organic extracts were washed with water (2 × 2 mL) and then dried over sodium sulfate. The solvent was removed in vacuo to afford 16 mg (92%) of crystalline material whose melting point and IR spectrum were identical with those of internal hemiacetal **8HA** isolated from photolysis of enone **8**.

Oxidation of Photoproduct 7CP to the Known Compound 10CP. Keto alcohol **7CP** (40 mg, 1.5 mmol) was added to a solution of 48 mg (2.2 mmol) of pyridinium chlorochromate in 5 mL of freshly distilled anhydrous methylene chloride, and the resulting mixture was stirred at room temperature for 3.5 h under nitrogen. The mixture was extracted with three 10-mL portions of ether, and the combined organic extracts were filtered through Florisil in a sintered-glass funnel. Removal of solvent in vacuo gave an off-white solid, which was recrystallized from low-boiling petroleum ether to afford 35 mg (88%) of colorless crystals whose melting point and IR spectrum were identical with those of diketone **10CP** obtained from the low-temperature, solution-phase photolysis of enedione **5**.[5]

Oxidation of Photoproduct 7CB to the Known Compound 10CB. The procedure described above was repeated with 10 mg (0.04 mmol) of photoproduct **7CB** and 13 mg (0.05 mmol) of pyridinium chlorochromate. The crystalline product thus obtained (8 mg, 80%) proved to be exactly identical (melting point, IR) to photoproduct **10CB** obtained by photolysis of enedione **5** in the solid state or in solution at elevated temperatures.[5]

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

Synthesis of *N*-(Alkyloxy)pyridine-2(1*H*)-thiones: Alkylations of the Ambident Nucleophile Pyridine-2(1*H*)-thione *N*-Oxide and Attempted Isomerizations of 2-(Alkylthio)pyridine *N*-Oxide

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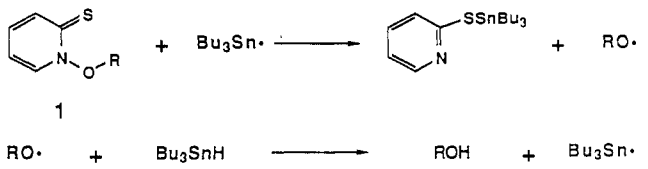
Two possible routes for the preparation of *N*-(alkyloxy)pyridine-2(1*H*)-thiones (**1**), namely, nucleophilic substitution of pyridine-2(1*H*)-thione *N*-oxide anion (**5**) and the thermal rearrangement of isomeric 2-(alkylthio)pyridine *N*-oxides (**6**), have been investigated. The ambident nucleophilic anion **5** undergoes both O- and S-alkylation upon treatment with alkyl bromides, chlorides, mesylates, or triflates; the regioselectivity is influenced by the temperature and the nature of the solvent, counterion, alkyl group, and leaving group. Details of the synthesis and characterization of a number of *N*-(alkyloxy)pyridine-2(1*H*)-thiones (**1**) (alkyl = *n*-propyl, *n*-butyl, benzyl, neopentyl, methoxymethyl, isopropyl, cyclopentyl, cyclohexyl, and *tert*-butyl) and 2-(alkylthio)pyridine *N*-oxides (**6**) (alkyl = *n*-propyl, *n*-butyl, and benzyl) are reported. Attempts to prepare **1** from the thermal rearrangement of **6** were unsuccessful, as **6** proved to be the thermodynamically stable isomer; the benzyl sulfide **1c** was converted into its isomer **6c** upon heating. Preliminary studies show that this rearrangement occurs in competition with N-O bond homolysis and appears to be catalyzed by molecular oxygen.

Introduction

Recently, we reported the use of *N*-(alkyloxy)pyridine-2(1*H*)-thiones (**1**) as sources of alkoxy radicals for mechanistic studies.[1,2] Reactions of **1** with an excess of tributylstannane, initiated either by heat and azobisisobutyronitrile or by irradiation with visible light, proceed in accordance with the radical chain mechanism shown in Scheme I. This manifold provides a suitable system for the measurement of the rates of rapid alkoxy radical rearrangements against the known rates of hydrogen abstraction from tributylstannane by alkoxy radicals.[3] The utility of this method has been demonstrated by the measurement of rate constants and Arrhenius parameters for the β-scission of the cyclopentyloxy radical.[2] The present work is concerned with the preparation of these novel alkoxy radical precursors.

Scheme I



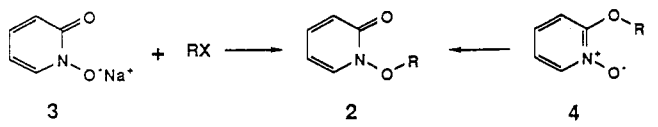
Prior to the mechanistic studies cited above, the synthesis and reactivity of **1** had not been reported, but a very similar class of compounds, the *N*-(alkyloxy)pyridin-2-(1*H*)-ones (**2**), had been prepared and studied.[4-6] In early

(1) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1988**, *110*, 4415.
(2) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230.
(3) (a) In ref 2 we used the estimated values of E_a = 1.83 ± 0.54 kcal/mol and $\log^{10} A$ = 9.70 ± 0.40 for the hydrogen abstraction from tributylstannane by the cyclopentyloxy radical. These estimates are in good agreement with the recent measurement of the corresponding Arrhenius parameters for the *tert*-butoxy radical: E_a = 1.1 ± 0.1 kcal/mol and $\log^{10} A$ = 9.5 ± 0.1.[3b] (b) Private communication with Dr. J. Lusztyk.

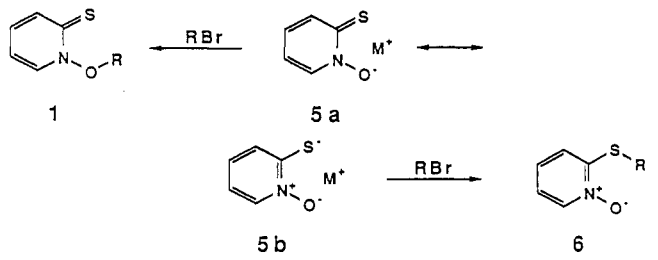
(4) (a) Shaw, E. *J. Am. Chem. Soc.* **1949**, *71*, 67. (b) Gardner, J. N.; Katritzky, A. R. *J. Chem. Soc.* **1957**, 4375.
(5) Schollkopf, U.; Hoppe, I. *Justus Liebigs Ann. Chem.* **1972**, *756*, 153.

0022-3263/89/1954-4330$01.50/0

Scheme II



Scheme III



studies **2** was prepared in 70–80% yield by nucleophilic substitution by the pyridin-2(1*H*)-one *N*-oxide anion (**3**) on some common alkylating agents. Thus the benzyl and methyl compounds (**2**, R = CH_3 or $PhCH_2$) were obtained by the reaction of the sodium salt of **3** with benzyl chloride and methyl tosylate, respectively.[4] Later work revealed that **2** could also be prepared in high yield from the thermal rearrangement of isomeric 2-alkoxypyridine *N*-oxides (**4**).[5,6] For example, heating a 0.5 M $CHCl_3$ solution of 2-ethoxypyridine *N*-oxide for 30 h at 140 °C afforded *N*-ethoxypyridin-2(1*H*)-one in 96% yield.[6] This isomerization route has been used to prepare most of the known derivatives of **2**. Mechanistic studies have shown that the isomerization is first order in [**4**], migration occurs with retention of configuration at the migrating carbon, the Hammet ρ value of migrating benzyl groups is –0.3, and the rate of isomerization is accelerated by the presence of conjugation in the migrating group.[6] It was concluded that a 1,4-sigmatropic rearrangement is the usual pathway for the isomerization of **4** to **2**. In a few cases, where the migrating group was severely sterically hindered or could form a stable radical, the rearrangement appeared to occur via a homolytic cleavage–recombination mechanism. In the present paper we examine the possibility of preparing *N*-alkoxypyridine-2(1*H*)-thiones (**1**) by routes analogous to those used for **2** (Scheme II).

Results

Since the sodium salt of pyridine-2(1*H*)-thione *N*-oxide (**5**, $M^+ = Na^+$) is readily available, our initial approach toward the preparation of **1** was by the reaction of **5** with alkyl halides. However, in preliminary experiments, the reaction of **5** with a variety of primary and secondary alkyl bromides (RBr) in DMF at 80 °C gave low yields of the desired product (5–15% from primary RBr and 25–40% from secondary RBr). The reason for the low yields of **1** has now been identified. In addition to the expected O-alkylation to give **1**, the major pathway under these reaction conditions (RBr + **5**, DMF, 80 °C) is S-alkylation to give 2-(alkylthio)pyridine *N*-oxide (**6**). This outcome is a reflection of the ambident nucleophilic character of the anion, pyridine-2(1*H*)-thione *N*-oxide (**5**) (Scheme III).

In order to elucidate the factors favoring O-alkylation, the product distributions of the reactions of *n*-propyl bromide, mesylate, and triflate and cyclopentyl bromide and mesylate with the pyridine-2(1*H*)-thione *N*-oxide anion (**5**) were examined as a function of the reaction conditions. The results are presented in Tables I and II. In all of these reactions, two isomeric products arising from O- and S-alkylation accounted for ≥95% of the starting material. Small amounts of cyclopentene (≤5% by GLC) were detected in the reactions of cyclopentyl substrates, demonstrating that elimination is only a minor pathway for this substrate.

In a second series of experiments, a number of *N*-(alkyloxy)pyridine-2(1*H*)-thiones (**1a–i**) were prepared by the reaction of alkyl bromides, chlorides, mesylates, and triflates with the tetraethylammonium salt of pyridine-2(1*H*)-thione *N*-oxide (**5**, $M^+ = Et_4N^+$) in DMF. The reaction conditions and isolated yields are presented in Table III. These compounds (**1a–i**) are either light yellow solids or, in a few cases, oils which slowly decompose in visible light. They are stable in the absence of light and are not readily attacked by oxygen or moisture (prolonged storage of the analytically pure oils at –5 °C sealed under air has resulted in a darkening of their color). Finally, three 2-(alkylthio)pyridine *N*-oxides (**6a–c**) were prepared from

Table I. Yields of *N*-(*n*-Propyloxy)pyridine-2(1*H*)-thione (1a) as a Function of Reaction Conditions[a]

counterion	leaving group	condtns	yield of 1a,[b] %
Na^+	Br	80 °C, DMF, 2 h	6
Na^+	Br	20 °C, DMF, 24 h	8
Et_4N^+	Br	20 °C, DMF, 24 h	14
Na^+	OMs	20 °C, DMF, 24 h	21
Et_4N^+	OMs	20 °C, DMF, 24 h	27
Na^+	OTf	20 °C, DMF, 1 h	28
Et_4N^+	OTf	–20 °C, DMF, 1 h	50
Et_4N^+	OTf	0 °C, DMF, 1 h	48
Et_4N^+	OTf	20 °C, DMF, 1 h	44
Et_4N^+	OTf	20 °C, DMSO, 1 h	29
Et_4N^+	OTf	20 °C, CH_2Cl_2, 1 h	16
Et_4N^+	OTf	20 °C, CH_3OH, 1 h	17

[a] The initial reactant concentrations were held constant at 0.20 M nucleophile + 0.20 M alkylating agent. [b] Yields of **1a** were determined by UV–vis.

Table II. Yields of *N*-(Cyclopentyloxy)pyridine-2(1*H*)-thione (1g) as a Function of Reaction Conditions[a]

counterion	leaving group	condtns	yield of 1g,[b] %	yield of C_5H_8,[c] %
Et_4N^+	Br	25 °C, DMF, 9 h	68	1.9
Et_4N^+	Br	50 °C, DMF, 2 h	67	2.4
Et_4N^+	Br	80 °C, DMF, 1 h	62	3.6
Na^+	Br	80 °C, DMF, 2 h	42	na
Et_4N^+	OMs	25 °C, DMF, 9 h	73	2.5
Et_4N^+	OMs	50 °C, DMF, 2 h	72	3.2
Et_4N^+	OMs	80 °C, DMF, 1 h	61	4.5
Et_4N^+	OMs	25 °C, DMF, 9 h	5	na

[a] The initial reactant concentrations were held constant at 0.20 M nucleophile + 0.20 M alkylating agent. [b] Yields of **1g** were determined by UV–vis. [c] Yields of C_5H_8 were determined by GLC (na = not analyzed).

Table III. Reaction Conditions and Isolated Yields of *N*-(Alkyloxy)pyridine-2(1*H*)-thiones from the Alkylation of 5 ($M^+ = Et_4N^+$) in DMF

compd	alkylating agent	condtns	mp, °C	yield, %
1a	*n*-PrOTf	0 °C, 1 h	oil	46
1b	*n*-BuOTf	0 °C, 1 h	oil	44
1c	BenzylOMs	0 °C, 1 h	74–77	26
1d	NeopentylBr	60 °C, 24 h	68–70	17
1e	MOMCl	40 °C, 1 h	57–59	31
1f	*i*-PrOMs	40 °C, 1 h	oil	54
1g	c-PentylOMs	40 °C, 1 h	42–44	66
1h	c-HexylBr	40 °C, 2 h	69–72	36
1i	*t*-BuBr	40 °C, 15 h	77–79	5

(6) (a) Dinan, F. J.; Tieckelmann, H. *J. Org. Chem.* **1964**, *29*, 1650. (b) Litster, J. E.; Tieckelmann, H. *J. Am. Chem. Soc.* **1968**, *90*, 4361.

Table IV. Isolated Yields of 2-(Alkylthio)pyridine *N*-Oxides from the Alkylation of 5 ($M^+ = Na^+$) in DMF

compd	alkylating agent	condtns	mp, °C	yield, %
6a	*n*-PrBr	80 °C, 2 h	62–64	89
6b	*n*-BuBr	80 °C, 2 h	70–72	87
6c	BenzylBr	80 °C, 2 h	168–169	96

the reaction of alkyl bromides with the sodium salt of pyridine-2(1*H*)-thione *N*-oxide (**5**, $M^+ = Na^+$) in DMF. The reaction conditions and isolated yields of these stable white crystalline compounds are presented in Table IV.

In order to determine if derivatives of **6** could be isomerized to **1** upon heating, solutions of **6a**, **6b**, and **6c** in diglyme were sealed either under vacuum or under air and then heated in the absence of light at 140 °C for 15 h. Comparison of the initial and final UV–vis spectra revealed no change in the starting material in every case.

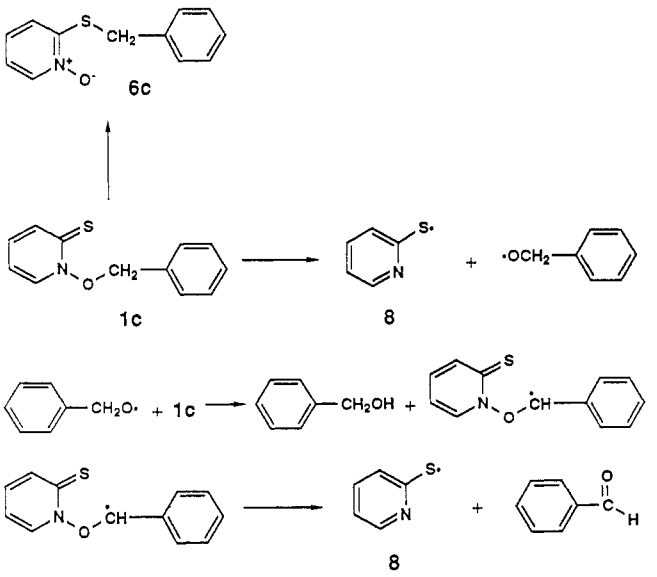
Further studies of the benzyl derivative **1c** were conducted in order to determine if the reverse reaction, **1c** to **6c**, would occur. A solution of **1c** in deuteriated benzene was sealed under vacuum and heated at 100 °C in the absence of light for 36 h. Analysis by ^1H NMR showed that 95% of the starting material had reacted, yielding a number of products, three of which were identified as **6c** (8%), benzaldehyde (40%), and benzyl alcohol (40%) by comparison with reference spectra. When the same solution of **1c** was sealed under air and heated at 100 °C in the absence of light, the reaction went to 95% completion in the much shorter time of 4 h. The same three products were formed, but now the distribution was **6c** (71%), benzaldehyde (6%), and benzyl alcohol (9%). The same procedure under an atmosphere of oxygen again resulted in 95% reaction within 4 h to afford **6c** (78%), benzaldehyde (5%), and benzyl alchol (6%).

Discussion

The results presented in Tables I and II demonstrate that the regioselectivity in the alkylation of **5** can be influenced to a large extent by the choice of solvent, counterion, and leaving group. Alkylation at the more electronegative, or harder, oxygen atom is favored over alkylation at the less electronegative, or softer, sulfur atom by the use of a polar aprotic solvent (DMF > DMSO > $CH_2Cl_2 \simeq CH_3OH$), a soft counterion ($Et_4N^+ > Na^+$), and a hard leaving group (OTf > OMs > Br). The reaction temperature causes only a minor effect, with the O:S alkylation ratio increasing slightly upon lowering the temperature. Examination of Tables I–III shows that the structure of the alkylating agent is also an important factor. When all other variables are held constant, it can be seen that secondary alkyl groups give higher yields of O-alkylation than primary ones. Competing elimination, which does not appear to be a major pathway with secondary alkyl groups under these reaction conditions, accounts for the low yield observed in the *tert*-butyl case.

These trends in reactivity conform to those documented for alkylations of other ambident nucleophiles,[7] e.g., enolate anions. Firstly, an ambident nucleophile is more likely to attack with the harder atom when it is the least encumbered by interactions with solvent molecules and counterions. This situation is best attained with a soft counterion in an aprotic polar solvent. Secondly, an ambident nucleophile is more likely to attack with the harder atom when the carbon center of the substrate is also hard, i.e., when the reaction becomes more S_N1-like in character. This situation is best attained with hard, strongly electron withdrawing leaving groups and with secondary, rather than primary, alkyl groups.

Scheme IV



The studies on the alkylation of **5** show that while it is possible to improve the yields of **1**, S-alkylation remains an important, and often the dominant, pathway in the reaction of **5** with the majority of alkylating agents that have been examined. Reaction conditions can be adjusted to afford **6** in high yield.

Given the known propensity of **4** to undergo thermal isomerization to **2**,[5,6] it was of interest to determine whether **6** would undergo an analogous 1,4-alkyl group migration to give **1**. However, when **6** (R = *n*-propyl, *n*-butyl, and benzyl) was heated under conditions known to cause the corresponding **4** to **2** isomerization, no reactions were observed. Even the benzyl compound **6c**, which would be expected to undergo migration more easily than the others, was found to be stable to heating at 140 °C for 15 h. In contrast, **4** (R = benzyl) is reported to afford the corresponding **2** in 92% yield upon heating at 100 °C for 2.5 h.[5a]

The fact that **4** is isomerized to **2** upon heating establishes **2** to be the more thermodynamically stable isomer. A possible explanation for the failure of **6** to isomerize to **1** is that the thermodynamic preference is reversed in these sulfur-containing analogues, an hypothesis supported by thermochemical data. Since there is little difference between the bond dissociation energies of RO—CH_2R and RS—CH_2R bonds (81 vs 77 kcal/mol, respectively),[8] the stabilities of the starting materials **4** and **6** should be very similar. However, there is quite a large difference in C=O and C=S bond energy (172 ± 3 kcal/mol in H_2C=O vs 129 ± 5 kcal/mol in H_2C=S)[9] and **2** is expected, therefore, to be much more stable than **1**.

If **6** is the thermodynamically stable isomer, then it should be possible to effect the isomerization of **1** to **6** upon heating. In fact, heating of **1c** in the absence of oxygen resulted in the formation of **6c** as a minor product together with benzaldehyde (40%) and benzyl alcohol (40%). These results are consistent with a 1,4-benzyl group migration in competition with N–O bond homolysis, with the latter pathway predominating. As shown in Scheme IV, subsequent reaction of the benzyloxy radicals would yield equal amounts of benzaldehyde and benzyl alcohol.

(7) (a) Marsh, J. *Advanced Organic Chemistry*; McGraw Hill: New York, 1977. (b) Le Noble, W. J. *Synthesis* **1970**, 1.

(8) Egger, K. W.; Cocks, A. T. *Helv. Chim. Acta* **1973**, *56*, 1516.

(9) Benson, S. W. *Chem. Rev.* **1978**, *78*, 23.

Further experiments revealed that the reaction time and product distribution were greatly altered when oxygen was present. The time required to effect 95% reaction decreased from 36 h under anaerobic conditions to 4 h in the presence of oxygen. The yield of **6c** increased from 8% (anaerobic) to 71% (under air) to 78% (under oxygen), while the combined yield of benzaldehyde and benzyl alcohol dropped from 80% to 15% to 11%. These results suggest that the 1,4-benzyl migration, **1c** to **6c**, is catalyzed by molecular oxygen.

While the full details concerning the mechanism of the reactions of **1c** await further investigation, these preliminary results are sufficient to show that **6** is thermodynamically favored over **1**. The fact that the benzyl group 1,4-migration is slow at 100 °C in the absence of oxygen establishes that such migrations do not occur during the alkylations of **5** that are carried out under nitrogen, at lower temperatures, and for shorter periods of time. Under these alkylation conditions, the O-alkylation product (**1**) is stable, and we conclude therefore, that the observed regioselectivity in the alkylations of **5** is a result of kinetic, rather than thermodynamic, control.

Conclusions

The experiments described above show that the pyridine-2(1*H*)-thione *N*-oxide anion behaves as an ambient nucleophile and undergoes reaction with suitable alkylating agents at both S and O. The relative extent of the two modes of alkylation is sensitive to temperature and to the nature of the solvent, counterion, alkyl group, and leaving group, with O-alkylation favored by the use of a dipolar aprotic solvent, soft counterion, and hard leaving group. However, even in the most favorable circumstances (the tetraethylammonium salt with a triflate or mesylate in DMF at room temperature or lower), the yield exceeds 55% only for the cyclopentyl compound and is very low for the *tert*-butyl and neopentyl compounds. While such yields may be adequate for the preparation of compounds required for kinetic studies, they are not sufficiently high for synthetic work. In a later paper, an alternative efficient approach to suitable precursors for alkoxy radicals will be described.

Experimental Section

General Procedures. Melting points were determined on a Reichert melting point apparatus and are uncorrected. Ultraviolet–visible (UV–vis) spectra were obtained in ethanol solution in 1-cm quartz cuvettes on a Varian DMS 90 spectrophotometer. Wavelength maxima (λ_{max}) are reported in nanometers. Extinction coefficients (ϵ, lit. mol^{-1} cm^{-1}) were obtained from plots of absorbance vs concentration over a concentration range of (0.1–2.0) $\times 10^{-4}$ M. Proton magnetic resonance (^{1}H NMR) spectra were, unless otherwise specified, obtained in $CDCl_3$ solution at 200 MHz on a JEOL JNM-FX200 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.00) as an internal standard. Multiplicities are abbreviated as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, m = multiplet. Mass spectra (MS) were recorded on a VG-Micromass 77F medium-resolution mass spectrometer operating at 70 eV. Masses are reported in units of mass over charge (m/z). Intensities are reported as a percent of the base peak intensity. The molecular ion is indicated by M. Microanalyses were carried out by the Analytical Laboratory at the Research School of Chemistry. Analysis by gas chromatography was performed on a Varian 3400 instrument with a 25-m phenyl methyl silicone capillary column, the response of the flame-ionization detector was calibrated with authentic compounds. Flash column chromatography was performed by using Ajax silica gel grade 923 (100–200 mesh).

N,*N*-Dimethylformamide (DMF) was distilled from calcium hydride and stored over 3-Å molecular sieves under nitrogen. Crystalline *N*-hydroxypyridine-2(1*H*)-thione and sodium pyridine-2(1*H*)-thione *N*-oxide (**5**, $M^+ = Na^+$) were prepared from a 40% aqueous solution of **5** ($M^+ = Na^+$) (trade name: sodium pyrion from Harcros Industrial Chemicals) as described previously.[10] Alkyl triflates were prepared by the reaction of the corresponding alcohol with triflic anhydride[11] and distilled immediately prior to use. Alkyl mesylates were prepared by the reaction of the corresponding alcohol with methanesulfonyl chloride[12] and, with the exception of benzyl mesylate (used in crude form), were distilled prior to use. Other alkylating agents, alkyl bromides and alkyl chlorides, were also distilled prior to use. All other commercially available reagents were used without further purification.

Preparation of Tetraethylammonium Pyridine-2(1*H*)-thione *N*-Oxide (5, $M^+ = Et_4N^+$). A 250-mL conical flask was charged with 25.0 g (0.20 mol) of *N*-hydroxypyridine-2(1*H*)-thione and 145 mL (0.20 mol) of a 20% aqueous tetraethylammonium hydroxide solution. After stirring for 0.5 h, a small amount of the acid remained undissolved and the pH of the solution was 6.5. The light yellow solution was filtered through a pad of charcoal on Celite to give a faint purple filtrate. The majority of the water was removed under reduced pressure at 40 °C to give a viscous oil. The remaining moisture was removed by forming an azeotrope with benzene; 100 mL of dry benzene was added to the residue and then removed on a rotary evaporator (water aspirator, 40 °C). This process was repeated twice more, and the resulting solid was dried (10^{-3} mmHg, 20 °C, 2 days) to yield 48 g (94%) of **5**, $M^+ = Et_4N^+$, as a white hygroscopic powder: mp (in a vacuum sealed capillary) 161–163 °C.

General Procedure for the Preparation of *N*-(Alkyloxy)pyridine-2(1*H*)-thiones 1a–i. A flame-dried round-bottomed flask equipped with a magnetic stirring bar was charged with tetraethylammonium pyridine-2(1*H*)-thione *N*-oxide (**5**, $M^+ = Et_4N^+$) and 25 mL of dry DMF per gram of **5** ($M^+ = Et_4N^+$). The flask was sealed with a rubber septum, and the contents were placed under an atmosphere of nitrogen. Due to the photolability of the desired product, the following manipulations were carried out under minimal lighting. The stirred suspension of **5** ($M^+ = Et_4N^+$) in DMF was brought to the desired temperature (immersion in an ice or oil bath), and 1 molar equiv of alkylating agent was added dropwise over a period of 15 min. After the addition, the mixture was stirred for an additional time period, becoming a clear yellow solution upon completion of the reaction. The temperature and time required to effect complete reaction depend upon the specific alkylating agent and are given in examples below. When the reaction was complete, the solvent was removed (10^{-3} Torr, 40 °C) and the residue was taken up in 10 mL of 0.1 M aqueous NaOH and 15 mL of ether per gram of **5** ($M^+ = Et_4N^+$) used. Any insoluble matter was removed by filtration as the two-phase mixture was transferred to a separatory funnel. The aqueous phase was extracted with ether until no further yellow color was observed in the ether layer. The combined ether extracts were washed with saturated aqueous $NaHCO_3$ and then with brine. Drying of the ether with $MgSO_4$ followed by evaporation of the solvent under reduced pressure gave crude product, which was purified by flash column chromatography (silica gel, ether) to afford pure product following drying (10^{-3} Torr, 20 °C, 24 h).

***N*-(*n*-Propyloxy)pyridine-2(1*H*)-thione (1a).** The reaction of 0.840 g (3.28 mmol) of **5** ($M^+ = Et_4N^+$) with 0.630 g (3.28 mmol) of *n*-propyl triflate in 25 mL of DMF at 0 °C for 1 h gave 0.255 g (46%) of **1a** as a light yellow oil: UV–vis λ_{max} 359 (ϵ 5250), 289 nm (11 400); ^{1}H NMR δ 1.08 (3 H, t), 1.89 (2 H, m), 4.39 (2 H, d), 6.24 (1 H, dt), 7.17 (1 H, dt), 7.67 (1 H, dd), 7.77 (1 H, dd); MS, m/z 169 (16, M) 127 (46, loss of $CH_3CH{=}CH_2$), 111 (100, loss of CH_3CH_2CHO). Anal. Calcd for $C_8H_{11}NOS$: C, 56.78; H, 6.55. Found: C, 56.52; H, 6.46.

***N*-(*n*-Butyloxy)pyridine-2(1*H*)-thione (1b).** The reaction of 4.51 g (17.6 mmol) of **5** ($M^+ = Et_4N^+$) with 3.63 g (17.6 mmol) of *n*-butyl triflate in 100 mL of DMF at 0 °C for 1 h gave 1.46

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g (44%) of **1b** as a light yellow oil: UV–vis λ_{max} 359 (ϵ 5520), 289 nm (11 800); ^{1}H NMR δ 0.99 (3 H, t), 1.53 (2 H, m), 1.79 (2 H, m), 4.42 (2 H, t), 6.61 (1 H, dt), 7.15 (1 H, dt), 7.65 (1 H, dd), 7.75 (1 H, dd); MS, m/z 183 (20, M), 127 (55, loss of $CH_3CH_2CH{=}CH_2$), 111 (100, loss of $CH_3CH_2CH_2CHO$). Anal. Calcd for $C_9H_{13}NOS$: C, 58.98; H, 7.15. Found: C, 58.98; H, 7.16.

***N*-(Benzyloxy)pyridine-2(1*H*)-thione (1c).** The reaction of 4.09 g (16.0 mmol) of **5** ($M^+ = Et_4N^+$) and 3.00 g (16.0 mmol) of benzyl mesylate in 100 mL of DMF at 0 °C for 1 h gave 0.91 g (26%) of **1c** as a yellow solid: mp 74–77 °C; UV–vis λ_{max} 361 (ϵ 5430), 289 nm (11 400); ^{1}H NMR δ 5.48 (2 H, s), 6.41 (1 H, dt), 7.11 (1 H, dt), 7.25–7.50 (6 H), 7.68 (1 H, dd); MS, m/z 217 (1.5 M), 111 (100, loss of C_6H_5CHO). Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45. Found: C, 66.18; H, 5.21; N, 6.52.

***N*-(Neopentyloxy)pyridine-2(1*H*)-thione (1d).** The reaction of 3.00 g (11.7 mmol) of **5** ($M^+ = Et_4N^+$) and 1.77 g (11.7 mmol) of neopentyl bromide in 50 mL of DMF at 60 °C for 24 h gave 0.38 g (17%) of **1d** as a yellow solid: mp 68–70 °C; UV–vis λ_{max} 361 (ϵ 5880), 289 nm (12 500); ^{1}H NMR δ 1.19 (9 H, s), 4.12 (2 H, s), 6.62 (1 H, dt), 7.14 (1 H, dt), 7.68 (2 H, m); MS, m/z 197 (2.5, M), 111 [100, loss of $(CH_3)_3CCHO$]. Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10. Found: C, 61.08; H, 7.76; N, 7.14.

***N*-[(Methoxymethyl)oxy]pyridine-2(1*H*)-thione (1e).** The reaction of 1.50 g (5.8 mmol) of **5** ($M^+ = Et_4N^+$) and 0.48 g (5.8 mmol) of methoxymethyl chloride in 25 mL of DMF at 40 °C for 1 h gave 0.31 g (31%) of **1e** as a yellow solid: mp 57–59 °C; UV–vis λ_{max} 360 (ϵ 6510), 289 nm (12 400); ^{1}H NMR δ 3.65 (3 H, s), 5.41 (2 H, s), 6.61 (1 H, dt), 7.18 (1 H, dt), 7.68 (2 H, m); MS, m/z 171 (16, M), 111 (100, loss of CH_3OCHO). Anal. Calcd for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18. Found: C, 49.35; H, 5.63; N, 8.15.

***N*-(Isopropyloxy)pyridine-2(1*H*)-thione (1f).** The reaction of 1.513 g (5.93 mmol) of **5** ($M^+ = Et_4N^+$) with 0.816 g (5.90 mmol) of isopropyl mesylate in 35 mL of DMF at 40 °C for 1 h gave 0.543 g (54%) of **1f** as a light yellow oil: UV–vis λ_{max} 360 (ϵ 5270), 298 nm (11 400); ^{1}H NMR δ 1.36 (6 H, d), 5.26 (1 H, m), 6.63 (1 H, dt), 7.18 (1 H, dt), 7.69 (2 H, m); MS, m/z 169 (2.5, M), 127 (63, loss of $CH_3CH{=}CH_2$), 111 [100, loss of $(CH_3)_2CO$]. Anal. Calcd for $C_8H_{11}NOS$: C, 56.78; H, 6.55. Found: C, 56.73; H, 6.48.

***N*-(Cyclopentyloxy)pyridine-2(1*H*)-thione (1g).** The reaction of 1.333 g (5.20 mmol) of **5** ($M^+ = Et_4N^+$) with 0.853 g (5.20 mmol) of cyclopentyl mesylate in 25 mL of DMF at 40 °C for 1 h gave 0.670 g (66%) of **1g** as a yellow oil, which crystallizes upon standing at −5 °C: mp 42–44 °C; UV–vis λ_{max} 360 (ϵ 5600), 289 nm (11 500); ^{1}H NMR δ 1.50–2.10 (8 H), 5.62 (1 H, m), 6.58 (1 H, dt), 7.14 (1 H, dt), 7.66 (2 H, m); MS, m/z 195 (1.0 M), 127 (51, loss of C_5H_8), 111 (100, loss of C_5H_8O). Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.51; H, 6.71; N, 7.17. Found: C, 61.14; H, 7.04; N, 7.08.

***N*-(Cyclohexyloxy)pyridine-2(1*H*)-thione (1h).** The reaction of 1.226 g (4.78 mmol) of **5** ($M^+ = Et_4N^+$) with 0.779 g (4.78 mmol) of cyclohexyl bromide in 25 mL of DMF at 40 °C for 2 h gave 0.361 g (36%) of **1h** as a yellow solid: mp 69–72 °C; UV–vis λ_{max} 360 (ϵ 5390), 289 nm (11 700); ^{1}H NMR δ 1.10–2.10 (10 H), 4.92 (1 H, m), 6.55 (1 H, dt), 7.12 (1 H, dt), 7.66 (2 H, m); MS, m/e 209 (0.5 M), 127 (45, loss of C_6H_{10}), 111 (100, loss of $C_6H_{10}O$). Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 63.24; H, 7.57; N, 6.69.

***N*-*tert*-Butoxypyridine-2(1*H*)-thione (1i).** The reaction of 2.82 g (11.0 mmol) of **5** ($M^+ = Et_4N^+$) with 1.51 g (11.0 mmol) of *tert*-butyl bromide in 50 mL of DMF at 40 °C for 15 h gave 0.11 g (6%) of **1i** as a yellow solid: mp 77–79 °C; UV–vis λ_{max} 361 (ϵ 5730), 289 nm (12 400); ^{1}H NMR δ 1.54 (9 H, s), 6.56 (1 H, dt), 7.10 (1 H, dt), 7.70 (2 H, m); MS, m/z 183 (13, M), 127 [100, loss of $(CH_3)_2C{=}CH_2$]. Anal. Calcd for $C_9H_{13}NOS$: C, 58.98; H, 7.15; N, 7.64. Found: C, 58.82; H, 7.42; N, 7.85.

General Procedure for the Preparation of 2-(Alkylthio)pyridine *N*-Oxides 6a–c. A flame-dried 50-mL round-bottom flask equipped with a magnetic stirring bar was charged with 1.00 g (6.70 mmol) of sodium pyridine-2(1*H*)-thione *N*-oxide (**5**, $M^+ = Na^+$) and 10 mL of DMF. The flask was sealed with a rubber septum, and the contents were placed under nitrogen and then heated to 80 °C by immersion in an oil bath. One molar equivalent of alkyl bromide was added via syringe, and the solution was stirred for 2 h. The DMF was then removed by rotary evaporation. The residue was stirred with 2 × 25 mL of $CHCl_3$, and the NaBr was removed by filtration. The $CHCl_3$ was removed by rotary evaporation. The residue was then stirred under 3 × 30 mL of refluxing pentane to remove the yellow O-alkylated impurity. The resulting white solid was then recrystallized from either ethyl acetate/hexane or benzene to afford pure product following drying (10^{-3} mmHg, 20 °C, 24 h).

2-(*n*-Propylthio)pyridine *N*-Oxide (6a). The reaction of 1.00 g (6.70 mmol) of **5** ($M^+ = Na^+$) with 0.824 g (6.70 mmol) of *n*-propyl bromide in 10 mL of DMF at 80 °C for 2 h gave 1.01 g (89%) of **6a** as a white crystalline solid (recrystallized from ethyl acetate/hexane): mp 62–64 °C; UV–vis λ_{max} 314 (ϵ 2470), 270 nm (8020); ^{1}H NMR δ 1.12 (3 H, t), 1.82 (2 H, m), 2.89 (2 H, t), 7.0–7.2 (3 H), 8.24 (1 H, d); MS, m/z 169 (41, M), 152 (100, loss of OH), 127 (98, loss of CH_3CH_2CHO). Anal. Calcd for $C_8H_{11}NOS$: C, 56.78; H, 6.55; N, 8.28. Found: C, 56.44; H, 6.80; N, 8.13.

2-(*n*-Butylthio)pyridine *N*-Oxide (6b). The reaction of 1.00 g (6.70 mmol) of **5** ($M^+ = Na^+$) with 0.918 g (6.670 mmol) of *n*-butyl bromide in 10 mL of DMF at 80 °C for 2 h gave 1.07 g (87%) of **6b** as a white crystalline solid (recrystallized from ethyl acetate/hexane): mp 70–72 °C; UV–vis λ_{max} 314 (ϵ 2490), 270 nm (7920); ^{1}H NMR δ 0.97 (3 H, t), 1.54 (2 H, m), 1.75 (2 H, m), 2.90 (2 H, t), 7.0–7.2 (3 H), 8.25 (1 H, d); MS, m/z 183 (8, M), 166 (31, loss of OH), 127 (100, loss of $CH_3CH_2CH{=}CH_2$), 111 (20, loss of $CH_3CH_2CH_2CHO$). Anal. Calcd for $C_9H_{13}NOS$: C, 58.98; H, 7.15; N, 7.64. Found: C, 58.85; H, 7.37; N, 7.55.

2-(Benzylthio)pyridine *N*-Oxide (6c). The reaction of 0.687 g (4.60 mmol) of **5** ($M^+ = Na^+$) with 0.787 g (4.60 mmol) of benzyl bromide in 10 mL of DMF at 80 °C for 2 h gave 0.960 g (96%) of **6c** as a white crystalline solid (recrystallized from benzene): mp 168–169 °C (lit.[13] mp 168–169); UV–vis λ_{max} 313 nm (ϵ 2580), 270 nm (8600); ^{1}H NMR δ 4.17 (2 H, s), 7.0–7.4 (8 H), 8.25 (1 h, d); MS, m/z 217 (8, M), 200 (100, loss of OH), 111 (6, loss of C_6H_5CHO). Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45. Found: C, 65.92; H, 5.21; N, 6.42.

Attempted Thermal Isomerizations of 6 to 1. In a typical experiment, a solution of 0.50 M **6** in diglyme was placed in an ampule and either frozen and flame-sealed under air or degassed (three freeze/pump/thaw cycles) and flame-sealed under vacuum.[14] The ampule was then heated at 140 °C for 15 h. The occurrence of any reaction was ascertained by comparison of initial and final UV–vis spectra. Regardless of whether sealed under a vacuum or under air, all three derivatives **6a**, **6b**, and **6c** gave final spectra that were superimposable upon the initial spectra.

Reactions of 1c at 100 °C. A solution of 0.50 M **1c** in deuteriated benzene was placed in ampules, which were then flame-sealed in one of three ways: under air, under oxygen, or degassed (three freeze/pump/thaw cycles) under vacuum. These samples were then heated in the absence of light at 100 °C, whereupon **1c** underwent reaction. In the presence of air or oxygen, the reaction was complete within 4 h. Upon cooling of these samples, a white precipitate formed, which was found to be identical with **6c**. In the absence of oxygen, the reaction was much slower, requiring 36 h for the disappearance of 95% of the starting material, and no precipitate formed upon cooling. The reaction solutions were diluted 1:1 with $CDCl_3$ containing TMS, which dissolved any **6c** that had precipitated. Proton NMR spectra of the initial solution (also diluted 1:1 with $CDCl_3$) and the three samples were recorded. Several products could be identified by comparison to spectra of authentic materials recorded in the same solvent mixture and quantified by using the TMS peak as an internal standard. These included **6c** (CH_2 singlet at 3.76 ppm), benzaldehyde (aldehyde singlet at 9.75 ppm), and benzyl alcohol (CH_2 singlet at 4.44 ppm).

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(14) The isomerizations were attempted in both the presence and absence of oxygen to ensure that the same conditions reported for the isomerizations of **4** to **2** were reproduced. In these reports,[5,6] the atmosphere under which the samples were sealed is not explicitly stated.