Deoxydative Thiation of 3-Substituted Pyridine *N*-Oxides with 4-Methoxytoluene-α-thiol: A Divergent Route to Pyridinethiols

Nobuhiro Sato* and Eiichi Nagano

Department of Chemistry, Yokohama City University, Yokohama 236, Japan

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Synthesis of 3-substituted 2-pyridinethiols was achieved by thiation of pyridine *N*-oxides with 4-methoxytoluene-α-thiol in the presence of diethylcarbamoyl chloride followed by cleavage of the resulting sulfides. The ease of substitution was shown to be affected by nucleophilicity of the *N*-oxide oxygen. Addition of zinc bromide to the reaction, a need for triethylamine, decreased most of the yield for thiation products but the formation of 3-methoxy-2-methoxybenzylthiopyridine was only improved. A plausible mechanism of the substitution, particularly β-thiation to the *N*-oxide function, is discussed compared with the regiochemistry observed in the reaction with diethoxyphosphoryl chloride instead of diethylcarbamoyl chloride. The debenzylation to pyridinethiol was also found to be dependent on the electron-density in the pyridine ring.

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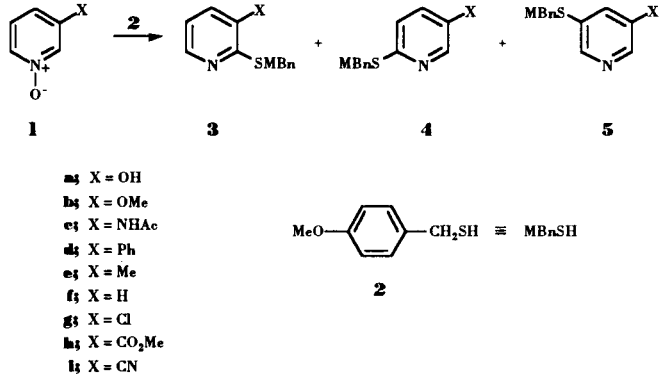
We recently reported deoxydative thiation of 3-substituted pyrazine 1-oxides with 4-methoxytoluene-α-thiol in the presence of diethylcarbamoyl chloride [1]. The resulting pyrazinyl methoxybenzyl sulfides were cleaved by mercuration and then by reduction to yield 3-substituted pyrazinethiols. Upon substitution and debenzylation reactions, their reactivities were found to be dependent on the substituent at C-3. Thus, an electron-donating group enhances reactions but an electron-withdrawing one suppresses them somewhat. Furthermore, the substitution was shown to be promoted by addition of zinc bromide to the reaction. During that research, we were interested in thiation of 3-substituted pyridine *N*-oxides using the same reagents because the substitution was expected to be more effected than the pyrazine series by inference from the less electron-deficient system of pyridine ring. As regarding deoxydative substitutions of pyridine *N*-oxides by thiols, an extensive investigation including the auxiliary reagents and bases has been made by Bauer and coworkers [2], in which there is precedent for reaction of the same class of *N*-oxides with 1-adamantanethiol in acetic anhydride [3]. We currently report not only the thiation by our reagent system but by comparison with the earlier ones.

Thiation of 3-substituted pyridine 1-oxides **1** was carried out by using 1.5 equivalents each of 4-methoxytoluene-α-thiol (**2**) and diethylcarbamoyl chloride in refluxing acetonitrile for 6 hours. Without added base, the reaction smoothly proceeded by the built-in diethylamine which was generated by the destruction of the departing diethyl carbamate ion (see Scheme 2). After workup, the isomeric products were isolated by chromatography or hplc if the separation was difficult by the former method. Identification of each component was conveniently achieved by their coupling constants between the ring protons in the ^{1}H nmr spectrum [4]. The results are summarized in Table 1. As can be seen, these *N*-oxides **1** are classified into three groups based on the reactivities, *i.e.*, most reactive *N*-oxides **1a** and **1b** giving more than 90% yields of sulfides, the secondary class of **1c-f** in the 70's% yields, and relatively less reactive group of **1g-i** in the 40's% yields. Those yields are approximately equal to those of the corresponding substituted pyrazine *N*-oxides [1]. Hence the thiation was affected in a similar fashion as in the pyrazine series [1], in other words, a key step in the substitution should involve nucleophilic attack of the *N*-oxide oxygen of **1** on diethylcarbamoyl chloride at the initial stage.

Scheme 1



Scheme 2

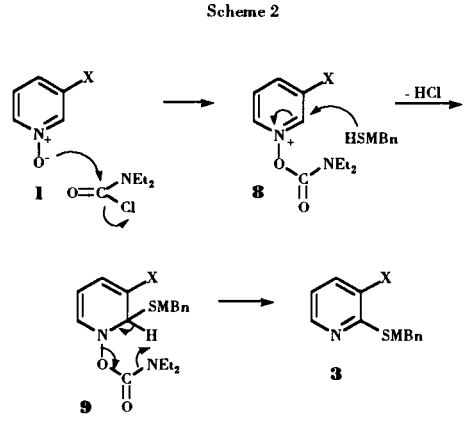


Table 1

Deoxydative Thiation of Pyridine *N*-Oxides **1a-i**

Substrate	Method [a]	Product and Yield (%)				Total Yield (%)
		3	**4**	**5**	**6**	
1a	A	92 [b]	0	0		92
	B	87 [c]	0	0		87
1b	A	62	10	21		93
	B	75	6	4		85
	C	43	7	8		58
	D	82	9	2		93
	E	42	12	≈0		54
1c	A	64	6	0		70
	B	40	9	0		49
1d	A	43	34	0		77
	B	43	47	0		90
1e	A	40	30	0		70
	B	25	27	0		52
1f	A	-65-		8		73
	B	-44-		[d]		>44
	D	-58-		19	1	78
	E	-69-		14	7	90
1g	A	36	5	3		44
	B [e]	30 [f]	13	4 [f]		47
1h	A	31	13	0		44
	B	16	9	0		25
1i	A	37	6	0		43
	B	15	0	0		15

[a] A: With thiol and acid chloride (1.5 molar equivalents each) in refluxing acetonitrile for 6 hours. B: With thiol, acid chloride (1.5 molar equivalents each) and zinc bromide (1.2 molar equivalents) in refluxing acetonitrile containing triethylamine (2.5 molar equivalents) for 6 hours. C: With thiol (1.1 molar equivalents) in acetic anhydride at 95-125° for 4 hours. D: With thiol (1.5 molar equivalents), and diethoxylphosphoryl chloride (3.5 molar equivalents) in refluxing acetonitrile containing triethylamine (5 molar equivalents) for 18 hours. E: With thiol (1.5 molar equivalents) and diethoxylphosphoryl chloride (3.5 molar equivalents) in refluxing acetonitrile containing DBU (5 molar equivalents) for 18 hours. [b] This is included a 7% yield of *O*-(diethylcarbamoyl) compound of **3a**. [c] The yield is contained with a 19% yield of the above product. [d] This compound could not be obtained by difficult separation with unidentified material. [e] A 2.2 molar equivalent of zinc bromide was used. [f] A small amount of unidentified 2,3- or 2,6-disubstituted pyridine was formed in addition.

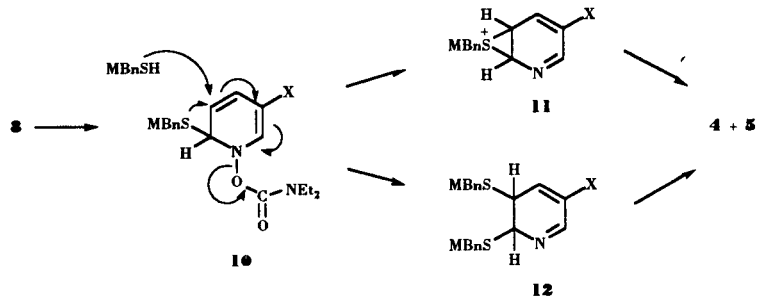
Expecting an improvement of the sulfide yields particularly from the less reactive class of *N*-oxides **1**, we attempted the thiation in the presence of zinc bromide in imitation of the Lewis acid-promoted substitution in pyrazine *N*-oxides [1]. Under identical conditions with those earlier [1], however, the desired products could not be obtained and the recovery of the starting *N*-oxide also failed. An inclusion of triethylamine in such a reaction brought about the thiation whereas the yields of sulfides were considerably lower than those without the zinc bromide in most cases. Since the base has a probable effect on the abstraction of hydrogen from the Meisenheimer intermediate **9** to the sulfide, it is suggested that zinc bromide coordinates strongly with **9** leading to a stable complex while the formation of **9** is rather accelerated by the Lewis acid. A difficult deprotonation is not exceptional as observed in deoxydative cyanation of 3-chloroquinoxaline 1-oxide with trimethylsilyl cyanide [5], in which the *N*-oxide was successfully cyanated only by employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a stronger base than triethylamine. The use of a large excess of the Lewis acid remarkably reduced the yields of sulfides except for **1g**.

As described above, the thiation of the *N*-oxides **1** with adamantanethiol in acetic anhydride has been accomplished by heating at 95-130° [3]. Compared with the present reactions with thiol **2**, the yields of adamantyl sulfides are influenced similarly by the substituent at C-3 but slightly lower than those of the corresponding substituted-pyrazinyl methoxybenzyl sulfides. The reactivity order in the reaction with adamantanethiol has been shown to be EtO > NHAc > OAc > Ph > H > Br, which is in agreement with that of *o,p*-directors in aromatic electrophilic substitution. An exception was thiation of 3-methylpyridine 1-oxide which gave relatively higher yield of the sulfides. These facts indicate that the substitution depends on the nucleophilicity of the *N*-oxide oxygen in the same manner as the current thiation with thiol **2**. On the other hand, 3-pyridinecarboxamide 1-oxide was converted into the adamantyl sulfides in higher yield than the parent pyridine 1-oxide **1f** and its 3-bromo derivative. The augmentation of reactivity is rationalized by an electron-withdrawing effect of the carbamoyl group to promote approach of the nucleophile to the *N*-acetoxypyridine intermediate. This behavior of a substituent is an interesting example because such a phenomenon could not be observed in the reaction of **1h** and **1i**, having 3-methoxycarbonyl and 3-cyano subtituents, respectively, with thiol **2**.

A nucleophilic attack of thiol **2** on the α-carbons to the *N*-carbamate function of intermediate **8** occurs preferentially at the *ortho* carbon C-2 to yield 2,3-disubstituted pyridines **3** as the main product. Conversely, 3-methoxycarbonyl or 3-(*N*-butylcarbamoyl) pyrazine 1-oxides underwent preferred α-thiation on the carbon *para* to the substituent producing 5-methoxybenzylthiopyrazinecarboxylic acid derivatives [1]. In the cases of **1d** and **1e** having phenyl and methyl substituents, respectively, a comparable amount of the 2,5-isomers **4** to that of **3** was formed. Analogous regioselectivities were reported in thiation of the identical *N*-oxides with adamantanethiol [3].

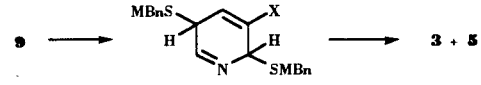
Although in low yield, the displacement on the β-carbon was observed for the thiation of pyridine *N*-oxides **1b**, **1f** and **1g**. The regiochemistry observed here is obviously different from that in the substitution of **1** with adamantanethiol [3], in which the *N*-oxides possessing phenyl (**1d**), methyl (**1e**) and bromo groups at C-3 be-

Scheme 3



sides the parent one (**1f**) underwent β-thiation in smaller amount. In this regard, it is noteworthy that treatment of **1b** with thiol **2** in acetic anhydride at 90-125° for 4 hours gave also the β-substituted product **5b** in 8% yield (see Table 1) unlike the reaction of 3-ethoxypyridine 1-oxide under identical conditions forming no β-adamantylthio compound [3]. It is implied that the sites of substitution are strikingly affected by the sulfur nucleophiles used. A proposed mechanism of the β-thiation involves a common intermediate for α-and β-substituted products, two types were devised *i.e.*, an episulfonium **11** [2,3] and a bimolecular-adduct **12** [6] or **13** [1]. As a matter of course, the annulation to the episulfonium intermediate from the 3-substituted pyridine *N*-oxides **1** requires the initial nucleophilic substitution with thiol **2** at the C-6 carbon. In contrast, formation of the bimolecular-adduct intermediate is not imposed by such a restriction, leading to either **12** or **13** according to the position of initial attack by thiol. To verify the pathway to **5**, we attempted the thiation of **1** with diethoxyphosphoryl chloride in the presence of triethylamine. This reagent system, which requires a longer period of the reaction, promotes only the abstraction of hydrogen on the final step to the α-substituted pyridines owing to the combined effect of the reinforcing diethylphosphate group and the base. Therefore, the regiochemistry which could be observed must reflect the situation prior to the second attack of the thiol **2**. In comparison with the thiation of **1b** with diethylcarbamoyl chloride, the total yield of sulfides and the portion of the α-substituted product **4b** are almost the same. However, the formation of the α-substituted product **3b** increased, which amount is in accord with the reducing one in the β-substituted pyridine **5b**. This fact is strongly denoted that the precursor of **5b** is the bimolecular-adduct intermediate **13**, and episulfonium **11** and other bimolecular-adduct intermediacies **12** are ruled out since both of them are generated from **10** (Scheme 3). On the thiation of pyridine *N*-oxides **1d** and **1e** with adamantanethiol in acetic anhydride [2,3], some highly substituted tetrahydropyridines which formed in addition to pyridyl sulfides were accounted as evidence of the episulfonium intermediate, but such products could not be detected from our procedure. Accordingly, the mechanism of substitution is likely different when the reagents-solvent system as the sulfur nucleophiles, auxiliary reagents and base is changed. Other proof will be required to establish a favorable intermediate for the present thiation.

Scheme 4



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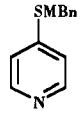
Unlike the product distributions in the thiation of **1b**, the reaction of the parent *N*-oxide **1f** with diethoxyphosphoryl chloride increased the proportion of the β-substituted pyridine **5f**. In view of the suppression of β-substituted 3-methoxypyridine **5b** as cited above, the majority of the 3-methoxybenzylthio product **5f** is thus formed *via* a common intermediate with the γ-substituted compound **6**. While deoxydative nucleophilic substitution of pyridine *N*-oxides, in general, substitutes both on the α- and γ-carbons to the *N*-oxide function, this latter displacement is almost preculuded in the 3-substituted *N*-oxides [7]. In the thiation of **1** with diethylcarbamoyl chloride, there was no instance of the formation of 4-substituted pyridines. That of **6** was realized only by diethoxyphosphoryl chloride as the auxiliary reagent, which was more evident by using DBU as the base. However, 4-methoxybenzylthio-3-methoxypyridine was not produced under even these same conditions. On account of an unlikely formation of the 3,4-disubstituted pyridines, γ-substitution is likely to be influenced by a steric environment in contrast to the facile occurrence of the α-substitution without being more hindered.



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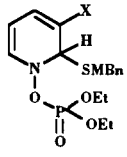
The effect of added DBU is opposite to that of triethylamine on the yields of sulfides between thiation of *N*-oxides **1b** and **1f** with diethoxyphosphoryl chloride.

This stronger base expedites the elimination of hydrogen from the intermediate **14f** leading to increased yields of the 2-substituted pyridine **3f**. Similarly, formation of the γ-substituted product **6** is accelerated by fast abstraction of hydrogen at H-4. However, DBU is more bulky than triethylamine so that the departure of diethylphosphoric acid from **14b** is suppressed to some extent due to the difficult approach of DBU by steric hindrance of the neighboring methoxy group. In the Lewis acid-mediated thiation of **1** except for **1b** and **1d**, the decrease in yields of **3** compared with those without zinc bromide may be also caused by a similar steric impediment by the substituent at C-3 on the aromatization of the pyridine ring with triethylamine. In the case of **1b**, the inclusion of triethylamine encouraged the formation of α-substituted products as cited above. As a result, the yield of **3** was improved though the combined yields of sulfides were decreased.



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Debenzylation of sulfides **3** was achieved by mercuration [8] and then by sodium borohydride reduction to give mercaptan **7**. These results are summarized in Table 2. As expected, the ease of S-C bond cleavage is influenced by the electron-donating effect of the 3-substituent except for the unsuccessful debenzylation of **3d** and **3h**. This fact exhibits that the reaction depends upon the nucleophilicity of the sulfide sulfur of **3** to mercury (II) acetate.

Scheme 5

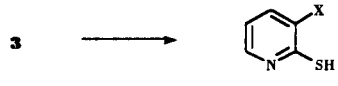

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Table 2

Preparation of Mercaptans **7** from Sulfides **3**

Sulfide	Mercaptan	Yield (%)
3a	**7a**	73
3b	**7b**	66
3c	**7c**	56
3d	**7d**	0
3e	**7e**	47
3f	**7f**	50
3g	**7g**	22
3h	**7h**	0
3i	**7i**	21

In conclusion, synthesis of 3-substituted pyridinethiols was accomplished by a two-step sequence of reactions starting from the corresponding substituted pyridine *N*-oxides. With regard to synthetic utility, mercaptans **7a**, **7b**, **7c** and **7f** are of practical use in view of the yield of the precursors of sulfides, the ease of separation and the successful debenzylation. These thiols are valuable for intermediates of chemotherapeutics [9], which have been previously prepared by reaction of halogenated pyridines with thiourea or alkali hydrosulfide under relatively severe conditions.

EXPERIMENTAL

All melting points were taken on a Büchi 535 apparatus and are uncorrected. The ir spectra were recorded on a JACSO IR-810 spectrometer. The ^1H and ^{13}C nmr spectra were measured in deuteriochloroform, unless otherwise noted, containing tetramethylsilane as the internal standard and recorded on a JEOL JNM EX270 instrument.

3-Methoxypyridine 1-Oxide (**1b**).

Ethereal diazomethane, prepared from *p*-tolylsulfonylmethylnitrosamide (21.5 g, 0.1 mole) by the usual method, was added to a stirred solution of 3-hydroxypyridine (3.40 g, 35 mmoles) in a mixture of methanol (45 ml) and water (5 ml) at 0°. After stirring at room temperature overnight, the resulting solution was evaporated *in vacuo*, and the residual oil was distilled at 87° (37 mm Hg) to give 3-methoxypyridine (2.25 g, 59%). This compound (20 mmoles) was dissolved in chloroform (30 ml) and 90% *m*-chloroperbenzoic acid (3.83 g, 20 mmoles) was added to it. The resulting solution was stirred at room temperature for 2 hours, then refluxed for 1 hour. After cooling, the mixture was washed with aqueous sodium carbonate and then water, dried and evaporated. The residue was recrystallized affording **1b** (2.00 g, 40% overall yield), as colorless needles, mp 99-100° (from ethyl acetate) (lit [10] mp 100-101°); ^1H nmr: δ 3.85 (3H, s), 6.88 (1H, ddd, J = 8.9, 1.7 and 0.7 Hz), 7.17 (1H, dd, J = 8.9 and 6.3 Hz), 7.90 (1H, ddd, J = 6.3, 1.7 and 0.7 Hz) and 7.98 (1H, t, J = 0.7 Hz).

The other *N*-oxides were prepared by oxidation of the corresponding substituted pyridines with peroxycarboxylic acid [11] except for commercially available **1e** and **1f**.

General Procedure of Thiation of Pyridine *N*-Oxides **1** with 4-Methoxytoluene-α-thiol (**2**).

An *N*-oxide **1** (1 mmole) and the mixture with zinc bromide (1.2 mmoles) was purged by passage of argon after evacuation of air, and then acetonitrile (7 ml), 4-methoxytoluene-α-thiol (**2**) (0.21 ml, 1.5 mmoles), and finally diethylcarbamoyl chloride (0.19 ml, 1.5 mmoles) was added *via* a syringe. The mixture was refluxed with stirring for 6 hours and then evaporated *in vacuo*. The residue was subjected to flash chromatography on silica gel (20 g) or to hplc equipped with the pre-packed column (2.2 x 30 cm, 10 μm silica gel), and eluted with hexane-ethyl acetate (10:1 to 3:1).

The following compounds were obtained by the above procedure.

3-Hydroxy-2-(4-methoxybenzylthio)pyridine (**3a**).

This compound was obtained from thiation of **1a** as colorless needles, mp 107-108° (from hexane); ir (potassium bromide): 1560, 1510, 1290, 1250, 1240 and 1180 cm^{-1} ; ^1H nmr: δ 3.78 (3H, s), 4.23 (2H, s), 6.76 (2H, d, J = 8.9 Hz), 7.02 (1H, dd, J = 8.3 and 4.6 Hz), 7.11 (1H, dd, J = 8.3 and 1.7 Hz), 7.17 (2H, d, J = 8.9 Hz) and 8.12 (1H, dd, J = 4.6 and 1.7 Hz); ^{13}C nmr: δ 37.1, 55.2, 114.0, 121.6, 123.0, 129.6, 129.9, 142.1, 143.4, 151.9 and 158.9.

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.14; H, 5.30; N, 5.66. Found: C, 63.29; H, 4.95; N, 5.53.

3-Methoxy-2-(4-methoxybenzylthio)pyridine (**3b**).

This compound was obtained from thiation of **1b** as colorless needles, mp 63-64° (from hexane); ir (potassium bromide): 1510, 1410, 1240, 1205, 1170 and 1090 cm^{-1}; ^1H nmr: δ 3.72 (3H, s), 3.79 (3H, s), 4.39 (2H, s), 6.79 (2H, d, J = 8.9 Hz), 6.89 (1H, dd, J = 8.3 and 1.7 Hz), 6.94 (1H, dd, J = 8.3 and 4.3 Hz), 7.33 (2H, d, J = 8.9 Hz) and 8.07 (1H, dd, J = 4.3 and 1.7 Hz); ^{13}C nmr: δ 32.6, 55.2, 55.6, 113.8, 115.0, 119.4, 130.0, 130.2, 140.7, 148.9, 152.0 and 158.6.

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.41; H, 6.10; N, 5.38.

3-Methoxy-5-(4-methoxybenzylthio)pyridine (**5b**).

This compound was obtained from thiation of **1b** as colorless prisms, mp 48.5-49° (from hexane); ir (potassium bromide): 1580, 1510, 1263, 1258, 1035 and 1030 cm^{-1} ; ^1H nmr: δ 3.76 (3H, s), 3.77 (3H, s), 4.06 (2H, s), 6.82 (2H, d, J = 8.9 Hz), 7.04 (1H, dd, J = 2.6 and 2.0 Hz), 7.18 (2H, d, J = 8.9 Hz), 8.12 (1H, d, J = 2.6 Hz) and 8.14 (1H, d, J = 2.0 Hz); ^{13}C nmr: δ 38.7, 55.5, 55.8, 114.0, 122.0, 128.7, 130.0, 133.5, 135.7, 143.0, 155.3 and 158.9.

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.54; H, 6.05; N, 5.35.

3-Acetamido-2-(4-methoxybenzylthio)pyridine (**3c**).

This compound was obtained from thiation of **1c** as colorless prisms, mp 108-109° (from hexane); ir (potassium bromide): 3230, 1660, 1510, 1390 and 1250 cm^{-1}; ^1H nmr: δ 2.14 (3H, s), 3.78 (3H, s), 4.41 (2H, s), 6.81 (2H, d, J = 8.6 Hz), 7.11 (1H, dd, J = 7.9 and 4.6 Hz), 7.24 (2H, d, J = 8.6 Hz), 7.33 (1H, br s), 8.29 (1H, d, J = 4.6 Hz) and 8.36 (1H, d, J = 7.9 Hz); ^{13}C nmr: δ 24.6, 35.6, 55.3, 114.0, 121.0, 128.0, 129.5, 130.1, 133.0, 144.9, 147.2, 159.0 and 168.6.

Anal. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.48; H, 5.59; N, 9.71. Found: C, 62.71; H, 5.48; N, 9.73.

2-(4-Methoxybenzylthio)-3-phenylpyridine (**3d**).

This compound was obtained from thiation of **1d** as colorless plates, mp 135° (from hexane); ir (potassium bromide): 1510, 1380, 1240, 1040 and 700 cm^{-1} ; ^1H nmr: δ 3.76 (3H, s), 4.37 (2H, s), 6.79 (2H, d, J = 8.9 Hz), 7.07 (1H, dd, J = 7.3 and 4.6 Hz), 7.29 (2H, d, J = 8.9 Hz), 7.38-7.42 (6H, m) and 8.46 (1H, dd, J = 4.6 and 2.0 Hz); ^{13}C nmr: δ 34.4, 55.2, 113.8, 119.2, 128.1, 128.4, 129.1, 129.9, 130.3, 135.7, 136.5, 138.1, 147.8, 157.5 and 158.6.

Anal. Calcd. for $C_{19}H_{17}NOS$: C, 74.24; H, 5.57; N, 4.56. Found: C, 74.26; H, 5.63; N, 4.63.

2-(4-Methoxybenzylthio)-5-phenylpyridine (**4d**).

This compound was obtained from thiation of **1d** as colorless needles, mp 124-125° (from hexane); ir (potassium bromide): 1510, 1460, 1250, 1240 and 1120 cm^{-1}; ^1H nmr: δ 3.78 (3H, s), 4.43 (2H, s), 6.84 (2H, d, J = 8.9 Hz), 7.22 (1H, dd, J = 8.2 and 0.7 Hz), 7.35 (2H, d, J = 8.9 Hz), 7.39-7.57 (5H, m), 7.68 (1H, dd, J = 8.2 and 2.3 Hz) and 8.69 (1H, dd, J = 2.3 and 0.7 Hz); ^{13}C nmr: δ 34.1, 55.3, 113.9, 121.9, 126.8, 127.8, 129.1, 129.8, 130.1, 132.7, 134.5, 137.6, 147.7, 157.8 and 158.7.

Anal. Calcd. for $C_{19}H_{17}NOS$: C, 74.24; H, 5.57; N, 4.56. Found: C, 74.27; H, 5.49; N, 4.56.

2-(4-Methoxybenzylthio)-3-methylpyridine (**3e**).

This compound was obtained from thiation of **1e** as a colorless oil, bp 150°/4 mm Hg (Kugelrohr); ir (neat): 1580, 1510, 1390, 1250 and 1080 cm^{-1}; ^1H nmr: δ 2.21 (3H, s), 3.76 (3H, s), 4.44 (2H, s), 6.83 (2H, d, J = 8.9 Hz), 6.92 (1H, dd, J = 7.6 and 4.9 Hz), 7.29 (1H, dd, J = 7.6 and 1.0 Hz), 7.35 (2H, d, J = 8.9 Hz) and 8.29 (1H, dd, J = 4.9 and 1.0 Hz); ^{13}C nmr: δ 18.5, 33.5, 55.2, 113.9, 119.1, 130.1, 130.2, 130.6, 136.2, 146.5, 158.0 and 158.7.

Anal. Calcd. for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.53; H, 6.17; N, 5.55.

2-(4-Methoxybenzylthio)-5-methylpyridine (**4e**).

This compound was obtained from thiation of **1e** as colorless prisms, mp 40-42° (from hexane); ir (potassium bromide): 1510, 1460, 1250, 1100 and 1030 cm^{-1}; ^1H nmr: δ 2.25 (3H, s), 3.76 (3H, s), 4.36 (2H, s), 6.82 (2H, d, J = 8.6 Hz), 7.05 (1H, dd, J = 7.9 and 0.7 Hz), 7.26 (1H, dd, J = 7.9 and 1.7 Hz), 7.31 (2H, d, J = 8.6 Hz) and 8.29 (1H, dd, J = 1.7 and 0.7 Hz); ^{13}C nmr: δ 17.8, 34.2, 55.2, 113.8, 121.8, 129.0, 130.0, 130.5, 136.9, 149.6, 155.4 and 158.6.

Anal. Calcd. for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.30; H, 6.24; N, 5.44.

2-(4-Methoxybenzylthio)pyridine (**3f** ≡ **4f**).

This compound was obtained from thiation of **1f** as colorless plates, mp 42.5-44° (from hexane); ir (potassium bromide): 1510, 1440, 1410, 1240 and 760 cm^{-1}; ^1H nmr: δ 3.80 (3H, s), 4.40 (2H, s), 6.83 (2H, d, J = 8.9 Hz), 6.98 (1H, ddd, J = 7.9, 5.0 and 1.7 Hz), 7.15 (1H, ddd, J = 7.3, 1.7 and 1.0 Hz), 7.33 (2H, d, J = 8.9 Hz), 7.46 (1H, ddd, J = 7.9, 7.3 and 1.7 Hz) and 8.46 (1H, ddd, J = 5.0, 1.7 and 1.0 Hz); ^{13}C nmr: δ 34.0, 55.2, 113.9, 119.5, 122.1, 129.9, 130.1, 135.9, 149.4, 158.7 and 159.1.

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.63; H, 5.51; N, 5.95.

3-Chloro-2-(4-methoxybenzylthio)pyridine (**3g**).

This compound was obtained from thiation of **1g** as colorless prisms, mp 44.5-46° (from hexane); ir (potassium bromide): 1510, 1380, 1250, 1030 and 780 cm^{-1}; ^1H nmr: δ 3.77 (3H, s), 4.40 (2H, s), 6.83 (2H, d, J = 8.9 Hz), 6.94 (1H, dd, J = 7.9 and 4.6 Hz), 7.34 (2H, d, J = 8.9 Hz), 7.51 (1H, dd, J = 7.9 and 1.3 Hz) and 8.35 (1H, dd, J = 4.6 and 1.3 Hz); ^{13}C nmr: δ 34.0, 55.2, 113.9, 119.7, 128.8, 129.3, 130.3, 135.7, 146.8, 157.4 and 158.8.

Anal. Calcd. for $C_{13}H_{12}NOSCl$: C, 58.75; H, 4.55; N, 5.27.

Found: C, 58.83; H, 4.31; N, 5.24.

5-Chloro-2-(4-methoxybenzylthio)pyridine (**4g**).

This compound was obtained from thiation of **1g** as colorless needles, mp 59-60° (from hexane); ir (potassium bromide): 1520, 1460, 1240, 1120 and 820 cm^{-1}; ^1H nmr: δ 3.78 (3H, s), 4.36 (2H, s), 6.83 (2H, d, J = 8.9 Hz), 7.10 (1H, d, J = 8.6 Hz), 7.30 (2H, d, J = 8.9 Hz), 7.43 (1H, dd, J = 8.6 and 2.3 Hz) and 8.41 (1H, d, J = 2.3 Hz); ^{13}C nmr: δ 34.3, 55.2, 113.9, 122.7, 127.9, 129.5, 130.1, 135.8, 148.0, 157.2 and 158.8.

Anal. Calcd. for $C_{13}H_{12}NOSCl$: C, 58.75; H, 4.55; N, 5.27. Found: C, 58.84; H, 4.17; N, 5.26.

Methyl 2-(4-Methoxybenzylthio)-3-pyridinecarboxylate (**3h**).

This compound was obtained from thiation of **1h** as colorless needles, mp 90-92° (from hexane); ir (potassium bromide): 1710, 1550, 1510, 1390, 1280 and 1240 cm^{-1}; ^1H nmr: δ 3.78 (3H, s), 3.90 (3H, s), 4.39 (2H, s), 6.83 (2H, d, J = 8.9 Hz), 7.06 (1H, dd, J = 7.9 and 4.6 Hz), 7.35 (2H, d, J = 8.9 Hz), 8.20 (1H, dd, J = 7.9 and 2.0 Hz) and 8.58 (1H, dd, J = 4.6 and 2.0 Hz); ^{13}C nmr: δ 34.3, 52.2, 55.2, 113.8, 118.3, 122.7, 129.7, 130.5, 138.8, 151.8, 158.6, 162.2 and 165.7.

Anal. Calcd. for $C_{15}H_{15}NO_3S$: C, 62.27; H, 5.23; N, 4.84. Found: C, 62.20; H, 5.26; N, 4.68.

Methyl 2-(4-Methoxybenzylthio)-5-pyridinecarboxylate (**4h**).

This compound was obtained from thiation of **1h** as colorless plates, mp 116-117° (from hexane); ir (potassium bromide): 1710, 1520, 1300, 1250 and 1130 cm^{-1}; ^1H nmr: δ 3.79 (3H, s), 3.90 (3H, s), 4.39 (2H, s), 6.82 (2H, d, J = 8.9 Hz), 7.06 (1H, dd, J = 8.3 and 0.7 Hz), 7.35 (2H, d, J = 8.9 Hz), 8.19 (1H, dd, J = 8.3 and 2.0 Hz) and 9.02 (1H, dd, J = 2.0 and 0.7 Hz); ^{13}C nmr: δ 33.9, 52.2, 55.3, 113.9, 121.1, 129.3, 129.4, 130.1, 130.5, 136.3, 150.7, 158.9 and 164.7.

Anal. Calcd. for $C_{15}H_{15}NO_3S$: C, 62.27; H, 5.23; N, 4.84. Found: C, 62.44; H, 5.03; N, 4.90.

3-Cyano-2-(4-methoxybenzylthio)pyridine (**3i**).

This compound was obtained from thiation of **1i** as colorless needles, mp 69-71° (from hexane); ir (potassium bromide): 2230, 1510, 1390, 1250 and 1030 cm^{-1}; ^1H nmr: δ 3.79 (3H, s), 4.47 (2H, s), 6.84 (2H, d, J = 8.9 Hz), 7.07 (1H, dd, J = 7.6 and 5.0 Hz), 7.34 (2H, d, J = 8.9 Hz), 7.78 (1H, dd, J = 7.6 and 1.7 Hz) and 8.60 (1H, dd, J = 5.0 and 1.7 Hz); ^{13}C nmr: δ 34.0, 55.3, 107.2, 114.0, 115.4, 118.6, 128.7, 130.3, 140.6, 152.0, 159.0 and 162.9.

Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.22; H, 4.60; N, 10.77.

The following materials could not be isolated or obtained in sufficient quantity for analysis so that only their nmr spectral data are given.

5-Methoxy-2-(4-methoxybenzylthio)pyridine (**4b**).

This compound was isolated from thiation of **1b** as the minor product; ^1H nmr: δ 3.77 (3H, s), 3.83 (3H, s), 4.32 (2H, s), 6.81 (2H, d, J = 8.9 Hz), 7.07 (1H, dd, J = 8.7 and 2.6 Hz), 7.09 (1H, dd, J = 8.7 and 1.3 Hz), 7.28 (2H, d, J = 8.9 Hz) and 8.20 (1H, dd, J = 2.6 and 1.3 Hz); ^{13}C nmr: δ 35.1, 55.2, 55.7, 113.8, 122.3, 123.3, 130.0, 130.1, 136.5, 149.3, 153.6 and 158.6.

5-Acetamido-2-(4-methoxybenzylthio)pyridine (**4c**).

This compound was the minor product which could not be isolated in the thiation of **1c**; ^1H nmr: δ 2.22 (3H, s), 3.90 (3H, s), 4.46 (2H, s), 6.80 (2H, d, J = 8.9 Hz), 7.16 (1H, d, J = 8.6 Hz), 7.28 (2H, d, J = 8.9 Hz), 7.40 (1H, br s), 7.88 (1H, dd, J = 8.6 and 2.3 Hz) and 8.42 (1H, d, J = 2.3 Hz).

3-(4-Methoxybenzylthio)pyridine (**5f**).

This compound was the minor product which could not be isolated in the thiation of **1f**; ^1H nmr: δ 3.78 (3H, s), 4.06 (2H, s), 6.81 (2H, d, J = 8.6 Hz), 7.16 (1H, dd, J = 7.9 and 5.0 Hz), 7.17 (2H, d, J = 8.6 Hz), 7.56 (1H, dt, J = 7.9 and 2.0 Hz), 8.42 (1H, dd, J = 5.0 and 2.0 Hz) and 8.52 (1H, d, J = 2.0 Hz).

4-(4-Methoxybenzylthio)pyridine (**6**).

This compound was the minor product which could not be isolated in thiation of **1f**; ^1H nmr: δ 3.79 (3H, s), 4.17 (2H, s), 6.86 (2H, d, J = 8.9 Hz), 7.11 (2H, dd, J = 4.6 and 1.7 Hz), 7.30 (2H, d, J = 8.9 Hz) and 8.36 (2H, dd, J = 4.6 and 1.7 Hz).

3-Chloro-5-(4-methoxybenzylthio)pyridine (**5g**).

This compound was the minor product which could not be isolated in thiation of **1g**; ^1H nmr: δ 3.79 (3H, s), 4.09 (2H, s), 6.83 (2H, d, J = 8.9 Hz), 7.19 (2H, d, J = 8.9 Hz), 7.54 (1H, t, J = 2.0 Hz) and 8.36 (2H, d, J = 2.0 Hz).

5-Cyano-2-(4-methoxybenzylthio)pyridine (**4i**).

This compound was the minor product which could not be isolated in thiation of **1i**; ^1H nmr: δ 3.80 (3H, s), 4.42 (2H, s), 6.82 (2H, d, J = 8.9 Hz), 7.22 (1H, dd, J = 8.6 and 1.0 Hz), 7.31 (2H, d, J = 8.9 Hz), 7.64 (1H, dd, J = 8.6 and 2.0 Hz) and 8.68 (1H, dd, J = 2.0 and 1.0 Hz).

General Procedure of Debenzylation of Pyridyl Methoxybenzyl Sulfide **3**.

A mixture of sulfide (0.5 mmole) in trifluoroacetic acid (6 ml) containing anisole (0.13 ml) was cooled at 0° with stirring, and mercury(II) acetate (0.159 g, 0.5 mmole) was added in small portions to it. The resulting mixture was stirred at 0° for 15 minutes and then evaporated at room temperature *in vacuo*. The residue was dissolved in 0.2N aqueous sodium hydroxide and then sodium borohydride (0.095 g, 2.5 mmoles) was added to it. After being stirred at room temperature for 1.5 hours, some insoluble matter was removed by filtration. The filtrate was acidified to *p*H 5 with acetic acid, and continuously extracted with chloroform for 24 hours. The crude product after evaporation was purified by chromatography on silica gel.

The following compounds were obtained by the above procedure.

2-Mercapto-3-pyridinol (**7a**).

This compound was obtained from debenzylation of **3a** as pale yellow prisms, mp 143.5-146° (from water) (lit [12] mp 144-145°); ir (potassium bromide): 3180, 1580, 1510, 1390, 1280, 1250 and 760 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 6.81 (1H, dd, J = 7.6 and 6.3 Hz), 7.13 (1H, dd, J = 7.6 and 1.3 Hz), 7.32 (1H, dd, J = 6.3 and 1.3 Hz), 7.73 (1H, br s) and 13.0 (1H, br s); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 115.5, 115.9, 127.4, 155.1

and 166.2.

Anal. Calcd. for C_5H_5NOS: C, 47.23; H, 3.96; N, 11.01. Found: C, 47.04; H, 4.05; N, 10.81.

3-Methoxy-2-pyridinethiol (**7b**).

This compound was obtained from debenzylation of **3b** as pale yellow prisms, mp 178.5-182° (from ethyl acetate); ir (potassium bromide): 1580, 1510, 1340, 1260, 1140, 1110, 1000 and 770 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.77 (3H, s), 6.77 (1H, dd, J = 7.9 and 5.9 Hz), 7.14 (1H, dd, J = 7.9 and 1.3 Hz), 7.35 (1H, dd, J = 5.9 and 1.3 Hz) and 13.5 (1H, br s); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 56.1, 117.1, 121.9, 140.9, 144.1 and 152.5.

Anal. Calcd. for C_6H_7NOS: C, 51.04; H, 5.00; N, 9.92. Found: C, 51.00; H, 4.96; N, 9.82.

3-Acetamido-2-pyridinethiol (**7c**).

This compound was obtained from debenzylation of **3c** as pale yellow needles, mp 183-188° dec (from water); ir (potassium bromide): 3230, 1670, 1580, 1520 and 1340 cm^{-1}; ^1H nmr: δ 2.30 (3H, s), 6.78 (1H, dd, J = 7.9 and 6.3 Hz), 7.38 (1H, dd, J = 6.3 and 1.3 Hz), 8.73 (1H, dd, J = 7.9 and 1.3 Hz), 9.28 (1H, br s) and 13.0 (1H, br s); ^{13}C nmr: δ 25.0, 77.2, 115.1, 123.4, 130.0, 138.9 and 169.6.

Anal. Calcd. for $C_7H_8N_2OS$: C, 49.98; H, 4.79; N, 16.65. Found: C, 50.07; H, 4.49; N, 16.68.

3-Methyl-2-pyridinethiol (**7e**).

This compound was obtained from debenzylation of **3e** as pale yellow needles, mp 170° dec (from ethanol) (lit [13] mp 172-173°); ir (potassium bromide): 1570, 1390, 1080 and 770 cm^{-1}; ^1H nmr: δ 2.44 (3H, s), 6.75 (1H, t, J = 6.6 Hz), 7.46 (1H, d, J = 6.6 Hz), 7.55 (1H, d, J = 6.6 Hz), and 14.0 (1H, br s); ^{13}C nmr: δ 21.6, 113.9, 134.5, 136.9, 141.0 and 176.4.

2-Pyridinethiol (**7f**).

This compound was obtained from debenzylation of **3f** as pale yellow prisms, mp 123-126° (from hexane/ethyl acetate) (lit [14] mp 130-132°); ir (potassium bromide): 1570, 1360, 1130 and 740 cm^{-1}; ^1H nmr: δ 6.79 (1H, ddd, J = 6.9, 5.0 and 1.3 Hz), 7.40 (1H, ddd, J = 8.6, 6.9 and 1.7), 7.58 (1H, ddd, J = 8.6, 1.3 and 1.0 Hz), 7.61 (1H, ddd, J = 5.0, 1.7 and 1.0 Hz) and 12.8 (1H, br s); ^{13}C nmr: δ 114.0, 133.9, 136.8, 137.8 and 176.7.

3-Chloro-2-Pyridinethiol (**7g**).

This compound was obtained from debenzylation of **3g** as pale yellow plates, mp 187-197° (from ethyl acetate) (lit [15] mp 197-206°); ir (potassium bromide): 1570, 1380, 1310, 1150 and 760 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.09 (1H, dd, J = 7.9 and 5.0 Hz), 7.78 (1H, dd, J = 7.9 and 1.7 Hz) and 8.16 (1H, dd, J = 5.0 and 1.7 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 120.8, 129.4, 137.0, 146.5 and 151.8.

3-Cyano-2-pyridinethiol (**7i**).

This compound was obtained from debenzylation of **3g** as yellow needles, mp 217-220° (from ethyl acetate); ir (potassium bromide): 2220, 1580, 1560, 1540, 1400 and 1320 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 6.87 (1H, dd, J = 7.9 and 6.3 Hz), 7.98 (1H, dd, J = 6.3 and 1.7 Hz), 8.10 (1H, dd, J = 7.9 and 1.7 Hz) and 14.0 (1H, br s); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 113.8, 114.6, 116.9, 144.5, 144.8 and 175.1.

Anal. Calcd. for $C_6H_4N_2S$: C, 52.92; H, 2.96; N, 20.57. Found: C, 53.29; H, 2.85; N, 20.30.

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