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Synthesis of 2-Methyl- and 2-Phenyl-5-thiopyridines

Neville Finch* and C. W. Gemenden

Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901

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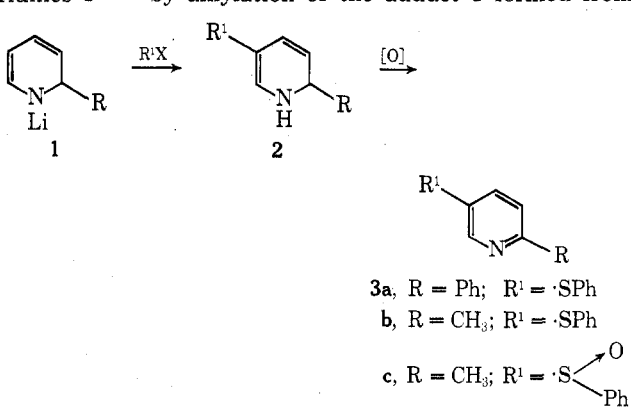
A new procedure is described for the "one pot syntheses" of 2-methyl- or 2-phenyl-5-methylthio-, butylthio-, or phenylthiopyridines, **3** and **4**. This involves formation of the pyridine/methyllithium (**1**, R = CH_3) or pyridine/phenyllithium (**1**, R = Ph) adduct and its reaction with the appropriate disulfide. While yields are low, work-up of the reaction in all cases is simple, and the 2,5-disubstituted product is obtained directly without position isomer problems. Use of the 5-butylthiopyridines **4b** and **4c**, *via* the Pummerer rearrangement of the sulfoxides **5b** and **5c**, as precursor for other 5-thiopyridines is described. An interesting formaldehyde trapping process is observed in one case where 2-phenyl-5-methylthiopyridine **4a** was used as such a precursor. Isolation of 2,5-dihydro-2-methyl-5-bis(phenylthio)pyridine (**9**) from the reaction of the pyridine/methyllithium adduct (**1**, R = CH_3) with phenyl disulfide and the isolation of 2-bis(*tert*-butylthio)methylpyridine from the reaction with *tert*-butyl disulfide suggested a mechanism for this "one pot synthesis" of 2-substituted-5-thiopyridines.

Reaction of the appropriate mercaptide anion with a 2- or 4-halopyridine provides ready access to the 2- and 4-thiopyridines.[1] Preparation of 3-thiopyridines by this procedure requires high temperatures, copper catalysis, and in most cases gives poor yields,[2] unless activating groups are appropriately positioned relative to the halogen, *e.g.*, as in 5-bromo-2-nitropyridine.[3]

A variety of alternative methods have been developed. Reduction of 3-pyridylsulfonyl chloride by stannous chloride[4] or red phosphorus and iodine[5] provides moderate yields of 3-pyridylthiol from which the ethers can be obtained by alkylation. Diazotization of 3-aminopyridine and reaction of the diazonium salt with a sulfur nucleophile gives the desired product, but in poor yield.[6,7]

More recently, use of thiocyanate as the nucleophile has been reported to give a 72% yield of 2-chloro-5-pyridylthiocyanate from 5-amino-2-chloropyridine *via* diazotization.[8] This procedure is the best reported to date. Reaction of pyridine *N*-oxide with benzenesulfonyl chloride and a thiophenol yields a mixture of 2- and 3-thiopyridines and appears to be of limited preparative value.[9]

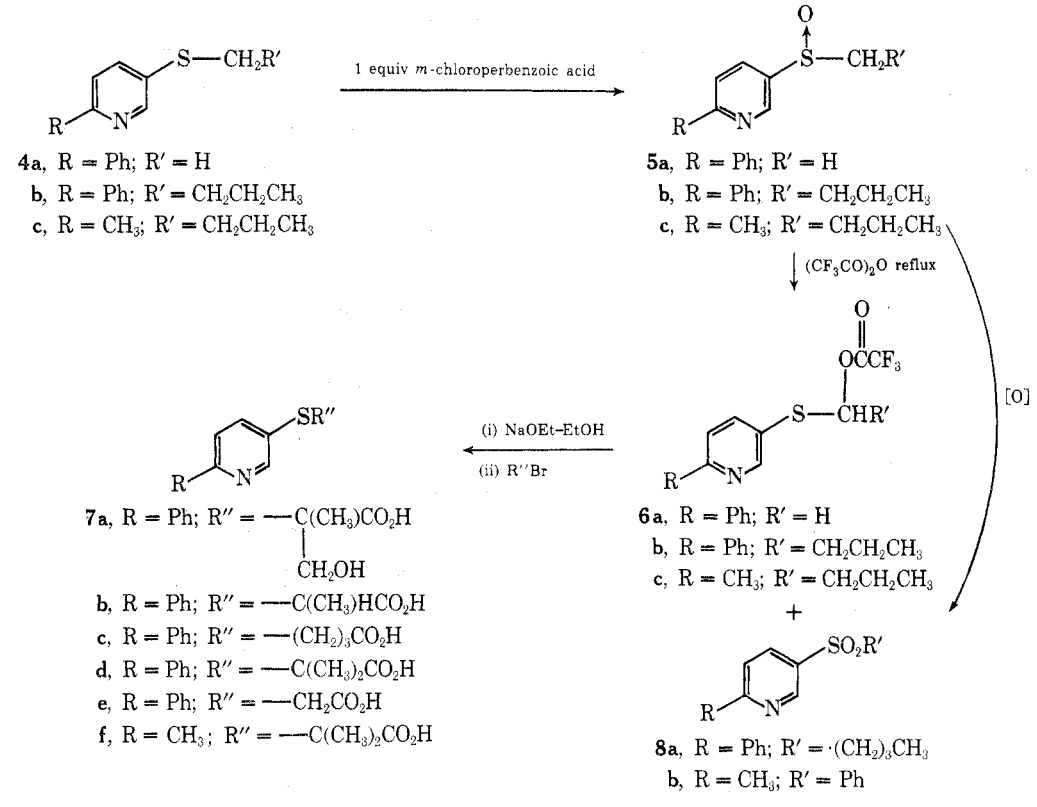
A need for 2-substituted 5-thiopyridines prompted us to develop a new synthetic procedure. We were attracted by recent reports of specific syntheses of 2,5-disubstituted pyridines **3**[10,11] by alkylation of the adduct 1 formed from



3a, R = Ph; R^1 = ·SPh
b, R = CH_3; R^1 = ·SPh
c, R = CH_3; R^1 = ·S(O)Ph

pyridine and an organolithium reagent. Such adducts 1 have been well characterized[12,13] and exclusively involve

Scheme I



addition to the 2 position. The striking feature of the chemistry of such adducts 1 is their reaction with most electrophiles exclusively at position 5 rather than at positions 1 and/or 3, although acylation does give substantial amounts of *N*-acylation.[14] The product obtained initially, *i.e.*, compound **2**, is a dihydropyridine. A mechanism by which intermediate **2** is oxidized to the final 2,5-disubstituted pyridine **3** has been suggested to be loss of lithium hydride.[15] Such a mechanism has been proposed for the aromatization of other dihydro heterocyclic aromatic systems.[16] Therefore, achievement of our goal should be possible by addition of a sulfur electrophile to the intermediate complex **1** formed from an appropriate organolithium reagent. Reaction of pyridine with phenyllithium to give **1** (R = Ph) and addition of benzenesulfenyl chloride gave a small yield of the desired 2-phenyl-5-phenylthiopyridine (**3a**). Since the use of a sulfenyl chloride perhaps favored reaction on nitrogen, as in the case of an acyl chloride,[14] we explored the use of diphenyl disulfide as the sulfur electrophile. The yield (29%) was still low, but acceptable in view of the simple isolation procedure which involved distillation of the crude reaction product. 2-Phenyl-5-phenylthiopyridine (**3a**) was the only isomer in the distillate and by-products were either much more volatile or were undistillable tars. That this product **3a** was a 2,5-isomer was immediately evident from the nmr spectrum. This spectrum showed only one low-field α-pyridyl proton (δ 8.78), which was a broadened singlet, *i.e.*, no ortho coupling. This was also true for the nmr spectrum of compound **4a;** however, in the nmr spectra other primary products **3b, 4b,** and **4c** meta splitting of the one low-field α-pyridyl proton could be seen, which provided additional support. As previous workers[12,13] have established that the addition of the organolithium reagent to the pyridine takes place at the 2 position, these spectral results indicate that reaction with electrophilic sulfur has also taken place at position 5.

To improve the utility of this synthesis, it was necessary that we provide a route to 2-substituted-5-pyridinethiols. Thus, substituents could be obtained at the 5 position, which would either not be accessible by the "one pot process" due to side reactions with the pyridine–lithium complex or because of the unavailability of the appropriate disulfide. It was envisioned that the thiol anion could be prepared *in situ* by collapsing a Pummerer rearrangement product **6** with sodium ethoxide (Scheme I) and then addition of the appropriate alkylating agent would give the desired product **7.** The initial choice of precursor for this process was 2-phenyl-5-methylthiopyridine (**4a**). Reaction of the pyridine adduct 1 (R = Ph) with methyl disulfide gave a low yield (17%) of the desired product (**4a**), but in this case it could be directly crystallized from the crude reaction mixture. Oxidation to the sulfoxide (**5a**) proceeded in 79% yield, without any concomitant oxidation of the pyridine nitrogen being evident. Reaction of the sulfoxide **5a** with refluxing trifluoroacetic anhydride gave a quantitative yield of the Pummerer product **6a,** which was used without further purification. Reaction of the Pummerer product **6a** with ethanolic sodium ethoxide at room temperature, followed by addition of ethyl 2-bromopropionate and heating, gave a crude ester which was hydrolyzed by aqueous base to a crystalline acid. This acid was not the expected product **7b,** but a product **7a** derived by trapping of the formaldehyde liberated on collapse of the Pummerer product **6a.** The desired product **7b** could be obtained by the simple expedient of removing the ethanol and then replacing it with fresh ethanol prior to addition of the alkylating agent. With the same process and use of ethyl 4-bromobutyrate, an excellent overall yield (87%) of the 4-(6-phenyl-3-pyridinylthio)butanoic acid (**7c**) could be obtained from the sulfoxide **5a.**

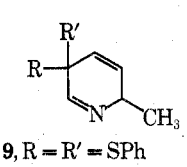
The additional step of removing the ethanol and formaldehyde after decomposition of the Pummerer product **5a** was troublesome for large scale use of the process, and other sulfoxides which would yield less reactive aldehyde

by-products were examined. Reaction of dibutyl disulfide with 1 (R = Ph) gave a 35% yield of 3-butylthio-6-phenylpyridine **4b,** which was readily isolated and then oxidized to the sulfoxide **5b** in 72% yield (Scheme I). Further oxidation of **5b** gave the sulfone **8a;** no oxidation at nitrogen was observed. As the sulfoxide **5b** and this sulfone **8a** had very different tlc behavior, this provided a simple analytical check on the quality of the sulfoxide **5b.** Reflux of the sulfoxide **5b** in trifluoroacetic anhydride yielded the Pummerer product **6b** which was treated with ethanolic sodium ethoxide at room temperature, followed by addition of the alkylating agent and warming. As expected, the butyraldehyde formed from **6b** does not interfere with the subsequent alkylation process, which therefore can be carried out from the sulfoxide **6b,** as we had originally intended from the sulfoxide **6a,** as a "one-pot" process. The overall yield of 2-methyl-2-(6-phenyl-3-pyridinylthio)propanoic acid (**7d**) from the sulfoxide **6b** using this process was 78%. Thus, we had achieved our goal of being able to vary widely the substituent on sulfur at position 5.

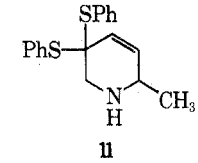
There remained a need for potential variation at position 2. Since 2-picolines can be transformed into a variety of functionalized pyridine derivatives,[17] reaction of the methyllithium–pyridine adduct 1 (R = CH_3) with phenyl and butyl disulfide was investigated. Reaction of butyl disulfide with the adduct 1 (R = CH_3) gave a comparable yield (27%) of 3-butylthio-6-methylpyridine (**4c**) to that obtained of **4b** from the phenyllithium adduct 1 (R = Ph). Oxidation with 1 equiv of *m*-chloroperbenzoic acid analogously yielded the sulfoxide **5c,** without competing reactions from the pyridyl nitrogen. However, unlike the sulfoxide of 3-butylthio-6-phenylpyridine (**5b**), this sulfoxide **5c** was thermally unstable; deterioration was observed on attempted chromatography and **5c** was therefore used directly from the reaction mixture. Reflux in trifluoroacetic anhydride converted it to **6c,** which was treated with ethanolic sodium ethoxide briefly at room temperature. Then the alkylating agent was added and the mixture warmed. Using ethyl 2-bromoisobutyrate as the alkylating agent and hydrolyzing the product gave 2-methyl-2-(6-methyl-3-pyridinylthio)propionic acid (**7f**) in 50% overall yield from the crude sulfoxide **5c.**

Reaction of the methyllithium–pyridine adduct 1 (R = CH_3) with phenyl disulfide gave only a small yield (8%) of the desired 2-methyl-5-phenylthiopyridine (**3b**), which could be also oxidized preferentially at sulfur by metachloroperbenzoic acid to give both the sulfoxide **3c** and the sulfone **8b** according to the amount of peracid added. A byproduct was also isolated in 1% yield from the reaction of phenyl disulfide with the adduct 1 (R = CH_3). This proved to be 2,5-dihydro-2-methyl-5,5-bis(phenylthio)pyridine (**9**), *i.e.,* the thioacetal of the ketone tautomer of 6-methyl-3-pyridinol! This was transformed by acid into the major product 2-methyl-5-phenylthiopyridine (**3b**). If the acid wash in the work-up of the reaction was omitted, **9** became the major product (11.5% yield) and could be isolated from the crude reaction mixture by direct crystallization. The nmr spectrum of this compound **9** showed the methyl group to be unusually shielded by a phenylthio group. Reduction of **9** by sodium cyanoborohydride yielded the tetrahydropyridine **11,** which is more conformationally mobile and showed the methyl resonance in the nmr at a normal position.

Isolation of such a compound as **9** sheds some light on the mechanism of this reaction and such dihydropyridines may be on the reaction pathway from **1** to **3** in the other examples we have described. Such dihydropyridines have not been isolated in previous studies of the reaction of **1** with other electrophiles.[10,11,14] The reason for this difference may be similar to that provided to explain that while enamines give exclusively monosubstituted products on alkylation or acylation, with sulfur electrophiles they give disubstituted products.[18] Further support for the view that such dihydropyridine compounds such as **9** are intermediates on the pathway to the final 2,5-disubstituted pyridines **3,** was obtained by the behavior of the methyl lithium–pyridine adduct 1 (R = CH_3) with *tert*-butyl disulfide. No 3-*tert*-butylthio-6-methylpyridine could be isolated; instead 2-bis(*tert*-butylthio)methylpyridine was the only isolable product. The identity of this material was confirmed by synthesis from 2-picoline. A plausible explanation for the appearance of this new reaction pathway is that the intermediate **2** (R′ = $SC(CH_3)_2CH_3$; R = CH_3) is too hindered at position 5 to react again with *tert*-butyl disulfide to give the crowded intermediate **10.** Instead, **2** is diverted onto polymeric materials or eliminates *tert*-butylthiol to give picoline *via* **12.**



9, R = R′ = SPh
10, R = R′ = S-C$(CH_3)_3$
12, R = H; R′ = SC$(CH_3)_3$



11

Experimental Section[19]

2-Phenyl-5-phenylthiopyridine (3a) *via* Phenylsulfenyl Chloride. Pyridine (3.95 g, 0.05 mol) was dissolved in ether (30 ml) and added dropwise with stirring to an ethereal solution of phenyllithium (25 ml of 1.3 *M* solution; 0.0325 mol) at room temperature. The mixture was stirred for 1 hr following addition and then cooled to −70°. A solution of phenylsulfenyl chloride (7.2 g, 0.05 mol) in an ether–benzene mixture was added dropwise . The mixture stirred at −70° for 2 hr and was allowed to come to room temperature overnight. The reaction mixture was diluted with ether and shaken with 2 *N* NaOH. The ether phase was extracted three times with 4 *N* HCl. The acid extract was made basic and reextracted with ether. Removal of the ether gave an oil (1.58 g). This was distilled in a Kugelrohr apparatus (130–170° (0.1 mm)). The bulk of the oil distilled to give a pale yellow oil which crystallized. This was recrystallized from ethanol to give 2-phenyl-5-phenylthiopyridine (**3a**): mp 58–60°; ir (Nujol) 1580 (m), 1552 (w), 735 (s), 690 (s) cm^{-1}; uv λ max (MeOH) 264 mμ (ε 15,440), 281 (15,030), 312 (10,600); nmr ($CDCl_3$) δ 8.78 (s, 1), 8.10–7.10 (m, 12).

Anal. Calcd for $C_{17}H_{13}NS$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.59; H, 5.17; N, 5.13.

2-Phenyl-5-phenylthiopyridine (3a) *via* Phenyl Disulfide. Pyridine (8.7 g, 0.11 mol) in benzene (50 ml) was added to phenyllithium (80 ml of 1.4 *M,* 0.11 mol) during 10 min. The mixture was then warmed at 50° for 1.5 hr. Phenyl disulfide (23.9 g, 0.11 mol) in benzene (100 ml) was added rapidly with stirring. The internal temperature rose to 64°. Heating was continued for 4 hr. Then the reaction was cooled to room temperature. Oxygen was bubbled through the reaction for 1.5 hr. The reaction was washed with water and brine and dried ($MgSO_4$). The benzene was removed *in vacuo.* The residue distilled in a Kugelrohr (130–170° (0.1 mm)). The main fraction (8.3 g, 0.0315 mol, 29%) crystallized and was recrystallized from ethanol to give 2-phenyl-5-phenylthiopyridine (**3a**) (5.5 g), mp 59–60°.

3-Methylthio-6-phenylpyridine (4a). Pyridine (158.2 g, 2.0 mol) was dissolved in benzene (500 ml) and added slowly with stirring to a solution of commercial phenyllithium (2.0 mol in 70:30 benzene–ether; Alfa) under nitrogen. After addition, the mixture was stirred at room temperature for 2 hr. Dimethyl disulfide (188 g, 2.0 mol) dissolved in benzene (250 ml) was added slowly with stirring and the mixture stood overnight at room temperature. The reaction mixture was washed with water and brine and dried ($MgSO_4$). The solvents were removed *in vacuo.* The residue, a red oil, was dissolved in ethanol, seeded, and cooled in the ice box. 3-

Methylthio-6-phenylpyridine (**4a**) (68 g, 0.34 mol, 17%): mp 92–94°; ir (Nujol) 1544 (m), 1108 (m), 1014 (m), 828 (m), 772 (m), 730 (s), 688 (m) cm^{-1}; uv λ max (MeOH) 244 mμ (ε 8,230), 280 (16,400); nmr ($CDCl_3$) δ 8.54 (s, 1), 8.1–6.9 (m, 7), 2.34 (s, 3).

Anal. Calcd for $C_{12}H_{11}NS$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.65; H, 5.60; N, 6.79.

3-Methylsulfinyl-6-phenylpyridine (5a). 3-Methylthio-6-phenylpyridine (**4a**) (18.5 g, 0.092 mol) was dissolved in methylene chloride (200 ml). With ice cooling and stirring, a solution of *m*-chloroperbenzoic acid (18.8 g, 0.097 *M*) in methylene chloride was added slowly. The mixture was stirred for 2 hr at room temperature following addition. No peracid was evident at this time based on starch iodide paper. The mixture was washed (2 × 10% aqueous $KHCO_3$ and water) and dried ($MgSO_4$) and the solvent was removed *in vacuo*. The solid remaining was recrystallized from 2-propanol–methylene chloride to give the sulfoxide **5a** (15.7 g, 79%): mp 128–130°; ir (Nujol) 1575 (m), 1556 (m), 1292 (m), 1048 (s), 1038 (s), 732 (m), 686 (m) cm^{-1}; uv λ max (MeOH) 258 mμ (ε 15,270), 286 (16,490); nmr ($CDCl_3$), δ 8.80 (d, 1 *J* = 2 Hz), 8.20–7.70 (m, 4), 7.43 (t, 3), 2.77 (s, 3).

Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.35, H, 5.10; N, 6.45. Found: C, 66.10; H, 5.39; N, 6.55.

Attempted *in Situ* Alkylation of 2-Phenyl-5-pyridylthiol *via* the Sulfoxide 5a. 3-Methylsulfinyl-6-phenylpyridine (**5a**) (6 g, 0.028 mol) was refluxed with trifluoroacetic anhydride (40 ml) for 2 hr. The material slowly dissolved during that time. The anhydride was removed *in vacuo*. The residue was dissolved in ether. The ether solution was washed (2 × 10% aqueous $KHCO_3$, brine) and dried ($MgSO_4$) and the ether was removed *in vacuo*. The trifluoroacetate **6a** (8 g) was checked by nmr (($CDCl_3$, δ 8.72 (m, 1), 8.10–7.60 (m, 4), 7.40 (t, 3), 5.50 (s, 2)) and dissolved in ethanol. Ethanolic sodium ethoxide was added (from dissolving 772 mg of sodium metal) and the mixture was stirred at room temperature for 3 hr. Ethyl 2-bromopropionate (5.4 g, 0.030 mol) was added and the mixture was warmed at 70° overnight. The ethanol was removed *in vacuo*. The residue was washed with ether. The ethereal washings were dried ($MgSO_4$) and the ether was removed *in vacuo* to give the crude ester as an oil (6.4 g, 70%). This was hydrolyzed by reflux in methanolic sodium hydroxide. The reaction was acidified and the precipitate collected and recrystallized from 2-propanol to give 3-hydroxy-2-methyl-2-(6-phenyl-3-pyridinylthio)propanoic acid (**7a**): mp 165–167°; mass spectrum *m/e* M^+ 289; ir (Nujol) 1688 (s), 1590 (m), 1580 (m), 1542 (w), 1030 (s), 856 (m), 778 (m), 736 (s), 690 (s) cm^{-1}; nmr (DMSO) δ 8.74 (br s, 1), 8.30–7.90 (m, 4), 7.50 (t, 3), 3.70 (q, 2, *J* = 2 Hz), 1.44 (s, 3).

Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.70; H, 5.30; N, 4.81.

2-(6-Phenyl-3-pyridinylthio)propanoic Acid (7b) *via* the Sulfoxide 5a. The crude trifluoroacetate **6a** (7 g, 0.023 mol) obtained as above was added to a solution of sodium metal (0.66 g, 0.023 mol) in ethanol (50 ml). The mixture was stirred for 2 hr at room temperature under nitrogen and then concentrated *in vacuo*. The residue was redissolved in ethanol and ethyl 2-bromopropionate (4.2 g, 0.023 mol) added. The mixture was heated overnight at 75°. The ethanol was removed *in vacuo*. The residue was shaken between ether and water. The ether was separated, dried ($MgSO_4$), and removed. The residue was refluxed for 5 hr in methanolic NaOH (40 ml of 1 *N* NaOH–40 ml of MeOH). The methanol was removed *in vacuo*. The aqueous residue was washed with ether, acidified (2 *N* HCl), and reextracted with ether. Removal of the ether *in vacuo* gave a solid which was recrystallized from 2-propanol to give 2-(6-phenyl-3-pyridinylthio)propanoic acid (**7b**) (3.4 g, 0.013 mol, 57%): mp 139–141°; ir (Nujol) 1712 (s), 1590 (m), 1582 (m), 1550 (m), 1326 (s), 1236 (s), 1180 (s), 1032 (m), 848 (m), 782 (m), 738 (m), 694 (m), 664 (m), 650 (m) cm^{-1}; nmr (DMSO) δ 8.70 (s, 1), 8.25–7.90 (m, 4), 7.48 (t, 3), 3.95 (q, 1, *J* = 7 Hz), 1.42 (d, 3, *J* = 7 Hz).

Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.70; H, 5.11; N, 5.13.

4-(6-Phenyl-3-pyridinylthio)butanoic acid (7c) was prepared in an analogous manner using ethyl 4-bromobutyrate as the alkylating agent. After acidification of the hydrolysis reaction mixture with 2 *N* HCl, 4-(6-phenyl-3-pyridinylthio)butanoic acid (**7c**) was obtained: mp 89–91° (87%); ir (Nujol) 1714 (s), 1544 (w), 1318 (m), 1198 (m), 772 (m), 728 (m), 680 (m) cm^{-1}; uv λ max (MeOH), 280 mμ (ε 15,950); nmr ($CDCl_3$) δ 8.68 (s, 1), 8.0–7.2 (m, 7), 2.97 (t, 2), 2.50 (t, 2), 2.00 (q, 2).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.90; H, 5.65; N, 5.53.

3-Butylthio-6-phenylpyridine (4b). Pyridine (15.8 g, 0.2 mol) was added slowly with stirring to commercial phenyllithium (125 ml of a 1.6 *M* solution, 0.2 mol) under nitrogen. A yellow solid separated. The mixture was stirred overnight at room temperature. Butyl disulfide (35.6 g, 0.2 *M*) was added slowly (exothermic). The mixture was stirred at room temperature for a further 6 hr, then washed with water and brine, and dried ($MgSO_4$). The solvents were removed *in vacuo*, and the residue was distilled. A forerun of butyl disulfide was obtained. The main fraction, bp 145–155° (0.1 mm) (16.8 g, 0.069 mol, 35%), crystallized on standing. This was recrystallized from 2-propanol to give 3-butylthio-6-phenylpyridine (**4b**) (10.6 g): mp 33–34°; ir (Nujol) 1574 (m), 1545 (m), 728 (s), 686 (s) cm^{-1}; uv λ max (MeOH) 247 mμ (ε 10,660), 281 (16,250); nmr ($CDCl_3$) δ 8.60 (d, 1, *J* = 2 Hz), 8.12–7.80 (m, 2), 7.68–7.24 (m, 5), 2.90 (t, 2), 1.90–1.10 (m, 4), 0.88 (t, 3).

Anal. Calcd for $C_{15}H_{17}NS$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.04; H, 6.89; N, 5.84.

3-Butylsulfinyl-6-phenylpyridine (5b). 3-Butylthio-6-phenylpyridine (**4b**) (20.2 g, 0.083 mol) was dissolved in methylene chloride (200 ml) and cooled in an ice bath. With stirring, a solution of *m*-chloroperbenzoic acid (16.2 g, 0.083 mol based on 88.5% peracid) in methylene chloride was added dropwise during 20 min. The mixture stirred for a further 30 min and then washed with 10% aqueous $KHCO_3$ and brine and dried ($MgSO_4$). Removal of the methylene chloride *in vacuo* gave a yellow oil, which slowly crystallized. This was recrystallized from ether to give the sulfoxide **5b** (15.4 g, 0.0595 *M*, 72%): mp 68–70°; ir (Nujol) 1580 (m), 1560 (m), 1296 (m), 1034 (s), 836 (m), 776 (m), 732 (s), 686 (m) cm^{-1}; uv λ max (MeOH) 260 mμ (ε 15,740), 287 (17,290); nmr ($CDCl_3$) δ 8.80 (s, 1), 8.26–7.74 (m, 4), 7.45 (t, 3), 2.92 (t, 2), 2.00–1.10 (m, 4), 0.92 (t, 3).

Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.50; H, 6.74; N, 5.31.

3-Butylsulfonyl-6-phenylpyridine (8a). The sulfoxide **5b** (11.9 g 0.046 mol) was dissolved in methylene chloride (100 ml) and cooled in an ice bath. *m*-Chloroperbenzoic acid (8.95 g, 0.046 *M* of a 88.5% peracid mixture) was dissolved in methylene chloride (200 ml) and added slowly with stirring. The mixture was allowed to stir overnight at room temperature, and then washed (aqueous 10% $KHCO_3$, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue (11.94 g) was recrystallized from ether to give the sulfone **8a** (10.1 g, 0.037 mol, 80%): mp 83–85°; homogeneous by tlc (silica gel GF eluted by $CHCl_3$–ethyl acetate 4:1) sulfoxide 3.0, sulfone 8.0; ir (Nujol) 1594 (m), 1560 (w), 1314 (m), 1154 (s), 1100 (m), 838 (m), 732 (s), 680 (m) cm^{-1}; uv λ max (MeOH) 260 mμ (ε 15,890), 286 (20,260); nmr ($CDCl_3$) δ 9.12 (d, 1 *J* = 3 Hz), 8.24–7.80 (m, 4), 7.52 (t, 3), 3.18 (t, 2), 2.00–1.10 (m, 4), 0.90 (t, 3).

Anal. Calcd for $C_{15}H_{17}NO_2S$; C, 65.44; H, 6.22; N, 5.09. Found: C, 65.11; H, 6.32; N, 4.92.

2-Methyl-2-(6-phenyl-3-pyridinylthio)propanoic Acid 7d *via* the Sulfoxide 5b. 3-Butylsulfinyl-6-phenylpyridine (**5b**) (6 g, 0.023 mol) was refluxed in trifluoroacetic anhydride (40 ml) for 3 hr. The anhydride was removed *in vacuo* and the residue was dissolved in ether. The ethereal solution was washed (10% aqueous $KHCO_3$, 2 *N* NaOH, brine) and dried ($MgSO_4$). The ether was removed *in vacuo* and the residue dissolved in ethanol and added to a solution of sodium metal (0.55 g, 0.024 mol) in ethanol. The solution was stirred for 2 hr at room temperature. Ethyl α-bromoisobutyrate (4.98 g, 0.025 mol) was added in ethanol and the mixture was refluxed overnight. The ethanol was removed *in vacuo*. The residue was dissolved in ether, washed with water and brine, and dried ($MgSO_4$). The ether was removed *in vacuo*. The residue was dissolved in ethanol (60 ml), and 2 *N* NaOH (30 ml) was added. The mixture was refluxed for 2 hr. The ethanol was removed *in vacuo*. The aqueous residue was slowly made acid with 2 *N* HCl. 2-Methyl-2-(6-phenyl-3-pyridinylthio)propanoic acid (**7d**) (4.90 g, 0.018 mol, 78%) separated as a crystalline solid: mp 178–180°; ir (Nujol) 2400–1900 (br m), 1690 (s), 1590 (m), 1582 (m), 1268 (s), 1168 (s), 858 (m), 804 (m), 778 (m), 738 (s) cm^{-1}; uv λ max (MeOH) 256 mμ (ε 17,170), 285 (15,260); nmr (DMSO) δ 8.70 (t, 1), 8.30–7.94 (m, 4), 7.50 (t, 3), 1.45 (s, 6).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.10; H, 5.71; N, 4.97.

(6-phenyl-3-pyridinylthio)acetic acid (7e) was prepared in an analogous manner using ethyl bromoacetate. On acidification of the hydrolysis reaction mixture with 2 *N* HCl, the hydrochloride salt of (6-phenyl-3-pyridinylthio)acetic acid (**7e**) separated: mp 214–216°; ir (Nujol) 1710 (s), 1594 (m), 1584 (m), 1532 (m), 1380 (s), 1276 (s), 1192 (s), 896 (m), 846 (m), 772 (m), 712 (m), 678 (m)

cm^{-1}; nmr (DMSO) δ 8.78 (d, 1 J = 2 Hz), 8.5–8.0 (m, 4), 7.60 (t, 3), 4.20 (s, 2).

Anal. Calcd for $C_{13}H_{11}NO_2S$·HCl ($\frac{1}{2}H_2O$): C, 53.64; H, 4.47; N, 4.81. Found: C, 53.19; H, 4.40; N, 4.63.

3-Butylthio-6-methylpyridine (4c). Pyridine (15.8 g, 0.2 mol) was added dropwise to an ethereal solution of methyllithium (131 ml of a 1.6 M solution, 0.2 mol) under nitrogen. The mixture stirred overnight at room temperature. Butyl disulfide (35.6 g, 0.2 mol) in tetrahydrofuran was slowly added with stirring. The mixture was stirred at room temperature for 6 hr, then washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was redissolved in ether and washed three times with 4 N H_2SO_4. The acid washings were made basic and reextracted with ether. Removal of the ether gave a red oil which was distilled. 3-Butylthio-6-methylpyridine (**4c**) was the major fraction (10.0 g, 0.055 mol, 27%): bp 84–8° (0.1 mm) ir (film) 2925 (s), 1584 (m), 1552 (w), 1478 (s), 1364 (m), 1020 (m), 822 (m) cm^{-1}; nmr ($CDCl_3$) δ 8.50 (d, 1, J = 3 Hz), 7.62 (d, 1, J = 3 Hz), 7.50 (d, 1, J = 3 Hz), 7.03 (d, 1, J = 7 Hz), 2.84 (t, 2), 2.50 (s, 3), 1.90–1.10 (m, 4), 0.88 (t, 3).

Anal. Calcd for $C_{10}H_{15}NS$: C, 66.27; H, 8.34. Found: C, 65.84; H, 8.66.

2-Methyl-2-(6-methyl-3-pyridinylthio)propanoic Acid (7f). 3-Butylthio-6-methylpyridine (**4c**) (56 g, 0.309 mol) was dissolved in methylene chloride (700 ml) and cooled in an ice bath. *m*-Chloroperbenzoic acid (66.3 g, 0.325 mol based on 88.5% peracid) was dissolved in methylene chloride (700 ml) and added during 1 hr with stirring. After stirring overnight, a negative starch–iodide reaction was observed. The reaction mixture was washed (10% aqueous $KHCO_3$, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue, an orange red oil, was checked by tlc (Silica gel GF eluted by $CHCl_3$–ethyl acetate 4:1), no starting material was evident. A portion of this crude sulfoxide **5c** (4.0 g, 0.020 M) in ether (50 ml) was refluxed with trifluoroacetic anhydride (30 ml) for 1.5 hr, then concentrated to dryness *in vacuo*. The residue was dissolved in ether. The ethereal solution was washed (water and brine), dried ($MgSO_4$), and removed *in vacuo*. The residue (5 g) was the Pummerer product **6c** based on: nmr ($CDCl_3$) δ 8.42 (d, 1 J = 2 Hz), 7.56 (pr of d, 1, J = 2 and 7 Hz), 6.98 (d, 1, J = 7 Hz), 5.96 (t, 1), 2.48 (s, 3), 2.06–1.10 (m, 4), 0.90 (t, 3). This residue was dissolved in ethanol (20 ml) and added to a solution of sodium metal (500 mg, 0.022 mol) in ethanol and stirred at room temperature for 1.5 hr. Ethyl 2-bromoisobutyrate (4.29 g, 0.022 mol) was added. The mixture was heated at 75° overnight. The ethanol was removed *in vacuo*. The residue was dissolved in ether. The ethereal solution was washed (water), dried ($MgSO_4$), and concentrated *in vacuo*. The residue (4.5 g) was dissolved in methanol (60 ml) and 20% aqueous KOH (20 ml) and refluxed for 6 hr. The methanol was removed *in vacuo;* the aqueous residue was washed with ether. The pH was adjusted to 6.5; a solid separated. The mixture was extracted ($CHCl_3$). The chloroform extracts were washed (water), dried ($MgSO_4$), and concentrated *in vacuo*. The crystalline residue (4.0 g) was recrystallized from 2-propanol to give 2-methyl-2-(6-methyl-3-pyridinylthio)propanoic acid (**7f**) (2.4 g, 0.011 mol, 50%): mp 195–197°; ir (Nujol) 1702 (s), 1592 (s), 1288 (s), 1172 (s), 1124 (s), 1038 (m), 838 (m), 812 (m), 724 (m) cm^{-1}; uv λ max (MeOH) 219 mμ (11,650), 266 (3,640); nmr ($CDCl_3$) δ 8.42 (d, 1, J = 2 Hz), 7.70 (pr of d, 1, J = 2 and 7 Hz), 7.22 (d, 1, J = 7 Hz), 2.48 (s, 3), 1.40 (s, 6).

Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.00; H, 6.22; N, 6.44.

2-Methyl-5-phenylthiopyridine (3b). Pyridine (7.9 g, 0.1 M) was dissolved in benzene (70 ml) and added dropwise to methyllithium (55 ml of a 2 M solution, 0.11 mol) under nitrogen. The mixture was stirred at room temperature for 1 hr. Phenyl disulfide (21.8 g, 0.1 mol) dissolved in benzene (80 ml) was added slowly with stirring. The mixture stirred overnight at room temperature. Oxygen was passed through the mixture for 1 hr and then it was washed (water, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was redissolved in ether and extracted with 4 N H_2SO_4. The acid washings were made basic and reextracted with ether. The ethereal extracts were washed (water), dried ($MgSO_4$), and concentrated *in vacuo*. The residue (4.2 g) was chromatographed on neutral III alumina, made up in hexane. The major fraction (1.62 g, 0.0081 M, 8%) eluted by benzene–hexane 1:1 was 2-methyl-5-phenylthiopyridine (**3b**) which was characterized as the crystalline hydrochloride: mp 137–139°; ir (Nujol) 2300–2000 (br m), 1604 (m), 1530 (m), 1342 (m), 1140 (m), 1020 (m), 840 (m), 756 (s), 692 (s) cm^{-1}; uv λ max (MeOH) 250 mμ (ϵ 22,570), 322 (4,950); nmr ($CDCl_3$) δ 8.5 (d, 1, J = 3 Hz), 7.54 (pr of d, 1, J = 3 and 7 Hz), 7.26 (s, 5), 7.06 (d, 1, J = 7 Hz), 2.50 (s, 3).

Anal. Calcd for $C_{12}H_{11}NS$·HCl: C, 60.58; H, 5.05; N, 5.89. Found: C, 60.80; H, 5.04; N, 5.76.

A minor fraction collected subsequently by benzene–hexane 1:1 elution (310 mg, 1.0 mmol, 1%) crystallized. Recrystallization from ethanol gave 2,5-dihydro-2-methyl-5,5-bis(phenylthio)pyridine (**9**): mp 93–95°; ir (Nujol) 1634 (m), 794 (m), 744 (s), 688 (m) cm^{-1}; uv λ max (MeOH) 244 mμ (ϵ 25,660); nmr ($CDCl_3$) δ 7.76 (br s, 2), 7.68–7.10 (m, 9), 5.66 (br s, 3), 3.24 (q, 1), 0.54 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{18}H_{17}NS_2$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.68; H, 5.73; N, 4.47.

2,5-Dihydro-2-methyl-5,5-bis(phenylthio)pyridine (9). Pyridine (82 g, 1.04 mol) was dissolved in benzene (400 ml) and added slowly to methyllithium (1 mol) with stirring under nitrogen. The mixture was stirred for two further hours after addition. Phenyl disulfide (218 g, 1 mol) in benzene (1 l.) was added slowly and the mixture was stirred overnight at room temperature. The mixture was washed (water, 2 N NaOH, water, brine), dried ($MgSO_4$) and concentrated *in vacuo*. The residue, a red-yellow oil (171 g) was dissolved in 2-propanol, cooled, and seeded. 2,5-Dihydro-2-methyl-5,5-bis(phenylthio)pyridine (**9**) (35.8 g, 11.5%), mp 91–94°, crystallized on standing.

1,2,5,6-Tetrahydro-2-methyl-5,5-bis(phenylthio)pyridine (11). 2,5-Dihydro-2-methyl-5,5-bis(phenylthio)pyridine (**9**) (10 g, 0.032 mol) was dissolved in methanol (160 ml) and sodium cyanoborohydride (2.02 g, 0.032 mol) dissolved in water (440 ml) at pH 6–7 added slowly with stirring. The pH of the reaction mixture was maintained between 6 and 7 by addition of acetic acid. After addition, the mixture was stirred overnight at room temperature. The mixture was concentrated *in vacuo*. The aqueous residue was made basic with ammonia and ether extracted. The ether extracts were washed with 2 N HCl. The acid washings were made basic with 20% aqueous KOH and reextracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue (9.09) was a pale yellow oil which crystallized on standing. This was recrystallized from ether to give 1,2,5,6-tetrahydro-2-methyl-5,5-bis(phenylthio)pyridine (**11**) (6.2 g, 0.0198 mol, 62%): mp 69–71°; ir (Nujol) 1582 (w), 1572 (w), 1306 (m), 1294 (m), 1174 (m), 1000 (m), 934 (m), 854 (m), 832 (m), 750 (m), 734 (s), 700 (m), 688 (s) cm^{-1}; uv λ max (MeOH) 225 mμ (ϵ 24,370), 264 (4310); nmr (C_6D_6) δ 7.82–7.42 (m, 4), 7.24–6.82 (m, 6), 5.78 (pr of m, 1, J = 8 Hz) 5.36 (pr of d, 1, J = 8 Hz), 3.80 (q, 2, J = 14 Hz), 3.20–2.70 (m, 1), 0.80 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{18}H_{19}NS_2$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.95; H, 6.37; N, 4.52.

2-Methyl-5-phenylsulfinylpyridine (3c). 2-Methyl-5-phenylthiopyridine (**3b**) (17.3 g, 0.086 mol) was dissolved in methylene chloride (300 ml) and *m*-chloroperbenzoic acid (16.8 g, 0.086 mol based on 88.5% peracid) added portion-wise with stirring during 2 hr. The mixture was stirred for a further 2 hr, then washed (10% $KHCO_3$, 2 N NH_4OH, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue, a red oil, was dissolved in 2-propanol, seeded, and cooled. The sulfoxide **3c** (8.0 g, 0.037 M, 43%) crystallized out: mp 63–64°; ir (Nujol) 1578 (m), 1554 (w), 1300 (m), 1048 (s), 1010 (m), 834 (m), 746 (m), 722 (m), 682 (m) cm^{-1}; uv λ max (MeOH) 231 mμ (ϵ 14,260), 267 (5500); nmr ($CDCl_3$) δ 8.70 (d, 1, J = 2 Hz), 8.00–7.00 (m, 7), 2.55 (t, 3).

Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.29; H, 5.21; N, 6.29.

2-Methyl-5-phenylsulfonylpyridine (8b). 2-Methyl-5-phenylthiopyridine (**3b**) (2.37 g, 0.0118 mol) was dissolved in methylene chloride (200 ml). *m*-Chloroperbenzoic acid (4.60 g, 0.0236 mol based on 88.5% peracid) was added portion-wise with stirring during 2.5 hr. The mixture was stirred overnight at room temperature. It was then washed (10% aqueous $KHCO_3$, NH_4OH, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue (2.38 g, 87%) was recrystallized from 2-propanol to give the sulfone **8b:** mp 114–116°; ir (Nujol) 1590 (m), 1300 (s), 1162 (s), 1118 (m), 732 (m), 722 (m) cm^{-1}; uv λ max (MeOH) 234 mμ (ϵ 16,500), 266 (6,260); nmr ($CDCl_3$) δ 9.00 (d, 1, J = 2 Hz), 8.17–7.17 (m, 8), 2.59 (s, 3).

Anal. Calcd for $C_{12}H_{11}NSO_2$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.87; H, 4.95; N, 5.96.

2-Bis(*tert*-butylthio)methylpyridine. 2-Picoline (9.3 g, 0.1 mol) in benzene (20 ml) was added dropwise during 5 min to a solution of methyllithium (61 ml of a 1.66 M solution, 0.1 mol) with stirring under nitrogen. After a further 5 min *tert*-butyl disulfide (17.8 g, 0.1 M) in benzene (20 ml) was added dropwise. The mixture stirred overnight at room temperature. It was washed (water,

2 N NaOH, brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue, a red oil (7.4 g), was chromatographed on neutral III alumina made up in pentane. Elution by pentane gave 2.11 g which was discarded. Elution by ether gave 2-bis(*tert*-butylthio)methylpyridine (3.05 g, 0.0113 mol, 11%) which was distilled in a short path apparatus: bp 80° (0.1 mm); ir (film) 1588 (s), 1568 (m), 1470 (s), 1432 (s), 1364 (s), 1154 (s), 990 (m), 742 (m), 718 (m) cm^{-1}; uv λ max (MeOH) 271 mμ (ε 4480); nmr ($CDCl_3$) δ 8.42 (broad d, 1, J = 6 Hz), 7.64 (m, 2), 7.10 (q, 1), 5.16 (s, 1), 1.28 (s, 18).

Anal. Calcd for $C_{14}H_{23}NS_2$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.40; H, 8.95; N, 5.22.

Pyridine (7.9 g, 0.1 *M*) was treated with methyllithium (78 ml of a 1.60 *M* solution, 0.12 mol) and *tert*-butyl disulfide (17.8 g, 0.1 mol) in an analogous manner. The bulk of the products were water soluble, presumably 2-picoline. The material eluted from neutral III alumina by ether (0.91 g, 0.0034 *M*, 3%) was identical (ir, nmr, mass spectrum) with 2-bis(*tert*-butylthio)methylpyridine prepared above. Comparison was also made by tlc (silica gel GF eluted by $CHCl_3$–ethyl acetate 4:1).

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Registry No.—**3a,** 53730-69-1; **3b** HCl, 53730-70-4; **3c,** 53730-71-5; **4a,** 53730-72-6; **4b,** 53730-73-7; **4c,** 53730-74-8; **5a,** 53730-75-9; **5b,** 53730-76-0; **5c,** 53778-52-2; **6a,** 53730-77-1; **6c,** 53730-78-2; **7a,** 53730-79-3; **7b,** 53730-80-6; **7c,** 53730-81-7; **7d,** 53730-82-8; **7e** HCl, 53730-83-9; **7f,** 53730-84-0; **8a,** 53730-85-1; **8b,** 53730-86-2; **9,** 53730-87-3; **11,** 53730-88-4; pyridine, 110-86-1; phenylsulfenyl chloride, 931-59-9; phenyl disulfide, 882-33-7; dimethyl disulfide, 624-92-0; *m*-chloroperbenzoic acid, 937-14-4; trifluoroacetic anhydride, 407-25-0; ethyl 2-bromopropionate, 535-11-5; ethyl 4-bromobutyrate, 2969-81-5; butyl disulfide, 629-45-8; ethyl α-bromoisobutyrate, 600-00-0; ethyl bromoacetate, 105-36-2; 2-bis(*tert*-butylthio)methylpyridine, 53730-89-5; 2-picoline, 109-06-8.

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New Fluorinating Reagents. Dialkylaminosulfur Fluorides[1]

William J. Middleton

Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

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Dialkylaminosulfur trifluorides (**2**) and bis(dialkylamino)sulfur difluorides (**5**) are easy to handle fluorinating reagents useful for replacing hydroxyl and carbonyl oxygen with fluorine under very mild conditions. The trifluorides (**2**) were prepared by the reaction of dialkylaminotrimethylsilanes (**1**) with SF_4, and the difluorides (**5**) were prepared by the reaction of **2** with **1**. These fluorides are particularly useful in fluorinating sensitive alcohols and aldehydes. For example, reaction of diethylaminosulfur trifluoride (DAST) with isobutyl alcohol gave isobutyl fluoride as the principal product, reaction of DAST with pivaldehyde at 25° gave $(CH_3)_3CCHF_2$ in 78% yield, and reaction of $Me_2NSF_2NEt_2$ with crotyl alcohol at 25° gave crotyl fluoride in 78% yield.

Sulfur tetrafluoride is a useful fluorinating agent for replacing oxygen with fluorine in organic compounds.[2] The substitution of one or two of the fluorine atoms in sulfur tetrafluoride with dialkylamino groups would result in aminosulfur fluorides that also may be expected to be fluorinating agents. We have examined the preparation and chemical properties of dialkylaminosulfur trifluorides and bis(dialkylamino)sulfur difluorides with the hope of developing new selective fluorinating reagents.

Preparation. The dialkylaminosulfur trifluorides (**2**) were prepared by an adaptation of a literature procedure,[3] which consists of treating sulfur tetrafluoride with a dialkylaminotrimethylsilane (**1**). Diethylaminosulfur trifluoride[4] (DAST), dimethylaminosulfur trifluoride,[3] and the new pyrrolidinosulfur trifluoride were prepared by this method. When this reaction is conducted in trichlorofluoromethane (bp 25°) at −70°, high yields of a product of very high purity are obtained, since the only appreciable by-product is fluorotrimethylsilane (**3**), an easily separated low-boiling (bp 17°) material. These three trifluorides are stable products that can be distilled and stored in plastic bottles at room temperature.

$$\underset{\mathbf{1}}{R_2NSi(CH_3)_3} + SF_4 \longrightarrow \underset{\mathbf{2}}{R_2NSF_3} + \underset{\mathbf{3}}{FSi(CH_3)_3}$$

Diisopropylaminosulfur trifluoride (**2**, R_2N = diisopropylamino) was also prepared, but it was unstable to distillation and decomposed to isopropyliminosulfur difluoride (**4**) when heated above 60°.

$$\underset{\mathbf{4}}{(CH_3)_2CHN{=}SF_2} \qquad \underset{\mathbf{5}}{R_2N{-}SF_2{-}NR'_2}$$

Bis(dialkylamino)sulfur difluorides (**5**) have not been prepared previously. We prepared them by the reaction of a dialkylaminotrimethylsilane (**1**) with a dialkylaminosulfur trifluoride (**2**) at 25°. The sulfur difluorides were not stable to distillation, but they could be easily purified by removing the volatile solvent (CCl_3F) and by-product (**3**) by evaporation at reduced pressure. The ^{19}F nmr spectra of