Experimental Section

General. All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 310B spectrometer; ^1H NMR spectra were obtained on a Varian A-60 spectrometer, and ^{13}C NMR spectra were recorded on a Varian XL-100 spectrometer. Mass spectra were obtained with a Hitachi RMU-60 spectrometer.

Cuprous Ferrocenyl Acetylide (6). The procedure used to prepare 6 was that used by Rosenblum et al.[13] with a 69% yield.

Ferrocenyl-*p*-methoxyphenylacetylene (7). The procedure followed was an adaptation of that by Stephens and Castro[14] in their synthesis of *p*-methoxydiphenylacetylene. In a typical preparation, 3.350 g (0.00143 mol) of *p*-iodoanisole was added to 50 mL of freshly distilled pyridine in a thoroughly dried 250-mL, three-neck, round-bottom flask which was fitted with a N_2 inlet, thermometer, and condenser leading to a mineral oil gas trap. Cuprous ferrocenyl acetylide (3.130 g, 0.0115 mol) was added in one portion to the pyridine solution. The resulting reaction mixture was allowed to stir for 10 h at 120 °C, after which time the solution had developed a dark red-brown color. After cooling, the reaction mixture was flooded with 250 mL of H_2O and extracted three times with 100-mL portions of ether. The combined ether extracts were washed successively with 10% aqueous HCl and 10% aqueous $NaHCO_3$ solutions. After drying over $MgSO_4$, the ether was removed via the rotary evaporator to yield a red-brown oil which solidified upon standing. The crude product was chromatographed from a basic alumina column with benzene to give 2.25 g (62%) of 7. When recrystallized from hexane, orange platelike crystals of 7 were obtained: mp 127–129 °C; IR 3100, 3000–2850, 1905, 1620, 1525, 1480, 1390, 1310, 1270, 1195, 1170, 1115, 1040, and 1010 cm^{-1}; ^1H NMR (CCl_3D) δ 3.8 (s, 3 H), 4.15–5.60 (m, 9 H), and 6.8–7.6 (m, 4 H); MS *m/e* 316 (M^+), 314, 301, 158, and 121; high resolution MS gave a mass for M^+ which corresponded to that of $C_{19}H_{16}OFe$ with a deviation of 0.0 ppm.

Ferrocenylacetylene (11). This compound was prepared from acetylferrocene via the method of Rosenblum et al.[13] with an overall yield of 82% and mp 53–54 °C (lit. mp 51–53 °C).

Hydration of Ferrocenyl-*p*-methoxyphenylacetylene (7). 7 (0.204 g) was added to a solution of 5 mL of acetic acid, 0.5 mL of H_2O, and 10 μL of concentrated H_2SO_4 under N_2. The resulting mixture was warmed to 75 °C for 6 h during which time there was a noticeable color change from orange to a dark red-brown. After cooling to room temperature, the reaction mixture was flooded with 25 mL of H_2O and extracted three times with 25-mL portions of CH_2Cl_2. The combined CH_2Cl_2 washings were combined, dried over $CaCl_2$, and evaporated on the rotary evaporator to yield 0.201 g (94%) of orange crystals, mp 90.5–91.5 °C. The hydration product was identified as ferrocenyl *p*-methoxybenzyl ketone by comparison of its IR, NMR, and melting point (91–92 °C) with that reported in the literature.[15]

Kinetic Data. Rates for the acid-catalyzed hydration reactions of 11 and 13 were obtained by using ^1H NMR to follow the disappearance of starting material. The reported rate constants represent the average of two separate runs with measurements being made at ten time intervals ranging through 3 half-lives. The solvent system used consisted of 5 mL of acetic-d_3 acid-*d*, 0.5 mL of D_2O, and 10 μL of concentrated H_2SO_4. Sufficient alkyne (11 or 13) was added to 0.40 mL of this solvent system to give a 0.50 M solution.

Compound 11 reacted so rapidly that significant reaction occurred during the time required for recording and integration of the appropriate peaks in its NMR spectrum. Thus the following method was employed to quench the reaction at precisely timed intervals. The requisite amount of 11 was dissolved in 5 mL of acetic-d_3 acid-*d* and 0.5 mL of D_2O, it having been determined that 11 did not undergo hydration in this solvent system. Reaction time was begun when 10 μL of concentrated H_2SO_4 was added to this solution. At precisely timed intervals, 0.4 mL of the reaction mixture was transferred with a syringe to NMR tubes containing 20 μL of pyridine, which instantly quenched the reaction. In this manner ten tubes representing ten different reaction times were prepared so that spectra and integration of each could be accurately recorded without error of further reaction.

Identification of Hydration Products (12 and 14). The hydration products listed in Table I were identified by comparison of NMR, IR, and melting point with those of authentic samples. Acetylferrocene (12) was synthesized via the method of Broadhead et al.[16] while *p*-methoxyacetophenone was purchased from Aldrich Chemical Co. (No. 11,737-4).

Registry No. 6, 53716-64-6; 7, 70659-04-0; 9, 55648-59-4; 11, 1271-47-2; 12, 1271-55-2; 13, 768-60-5; 14, 100-06-1; *p*-iodoanisole, 696-62-8.

(13) M. Rosenblum, N. Brawn, J. Papenmeier, and M. Applebaum, *J. Organomet. Chem.*, 6, 173 (1966).
(14) R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 28, 3313 (1963).
(15) T. A. Woods, T. E. Boyd, E. B. Biehl, and P. C. Reeves, *J. Org. Chem.*, 40, 2416 (1975).
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Convenient Method for the Synthesis of 25-Hydroxyvitamin D_3 Analogue. Structure Determination of Tertiary Alcohols by Carbon-13 Nuclear Magnetic Resonance Spectroscopy

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The biological importance of 25-hydroxyvitamin D, and its utilization as an intermediate for the synthesis of the medically useful 1α,25-dihydroxyvitamin D,[1] has been an incentive to search for its convenient synthesis.[2]

Most methods for the preparation of these metabolites use as starting materials naturally occurring sterols possessing an unsaturated side chain, which is degraded and rebuilt to give the side chain substituted cholesterol derivative.[3] In order to obtain the vitamin D system, it is necessary to convert the cholesterol derivative to the respective 5,7-diene which is then irradiated and thermally equilibrated.[4]

(1) Cf. H. F. DeLuca and H. K. Schnoes, *Annu. Rev. Biochem.*, 45, 631 (1976); D. R. Fraser and E. Kodicek, *Nature (London)*, 288, 764 (1970), and references cited therein.
(2) P. E. Georghiou, *Chem. Soc. Rev.*, 83 (1977).
(3) D. M. Piatak and J. Wicha, *Chem. Rev.*, 78, 199 (1978).
(4) L. F. Fieser and H. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, pp 91–168; G. M. Sanders, J. Pot, and E. Havinga, *Fortschr. Chem. Org. Naturst.*, 27, 131 (1969).

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Table I.
^{1}H Chemical Shifts[a] of CH_3 for Hydrindan 1b and Its Hydroxylated Analogues 2b, 3, 4, and 5

compd	H at C18	H at C26, 27
1b	0.87	0.85 d
2	0.88	1.21 s
3	0.84	0.85 d
4	0.98	0.85 d
5[b]	1.04	0.86 d

[a] Shifts are given relative to Me_4Si in ppm. [b] ^{1}H at C21 appears at 1.25 ppm.

The main drawback in these synthetic schemes is the photochemical step, which produces low yields of the unstable previtamin. Therefore, it was desirable to search for a different approach. The most convenient procedure might have been the direct hydroxylation of the easily accessible vitamin D_3 at C-25, which, however, proved unsuccessful. We therefore attempted to hydroxylate the side chain of the hydrindan derivative **1b**[5,6] obtained by oxidative cleavage of vitamin D_3, which can be easily reconverted to the vitamin system.

The starting material was prepared by vitamin D_3 ozonolysis followed by decomposition of the ozonide with lithium aluminum hydride and acetylation of the resulting alcohol.[5]

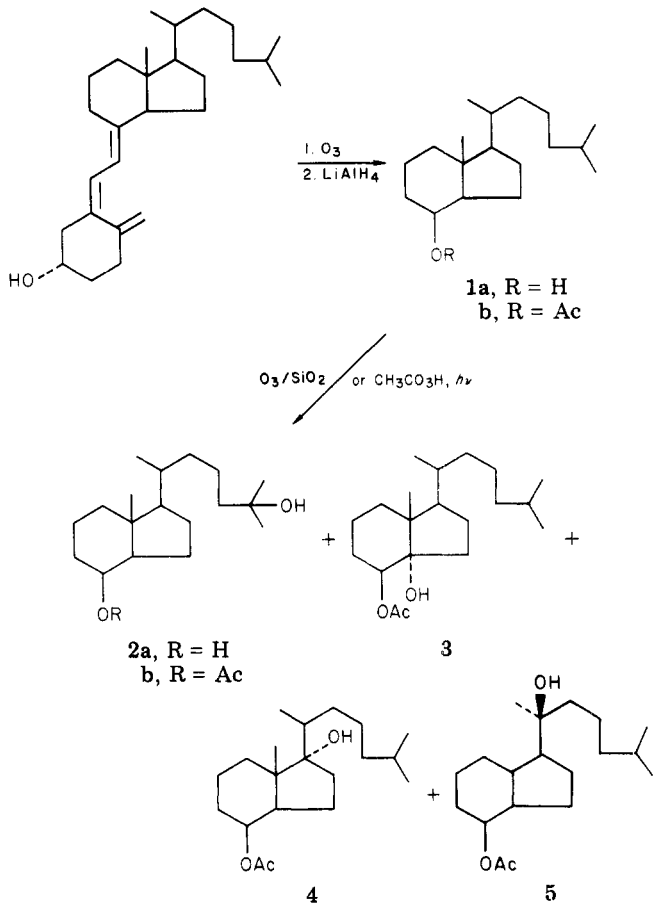
We have used three methods previously developed by us for the functionalization of this intermediate: dry ozonation,[7] peracetic acid oxidation,[8] and chlorination[9] with *N,N*-dichlorourethane.

Peracetic Acid Oxidation. The hydrindan derivative **1b**[5] in ethyl acetate was irradiated with 300-nm light in the presence of peracetic acid for 17 h, by which time all the acid decomposed. The irradiation was continued for another 10 h with an additional portion of the reagent. Chromatography on silica gel resulted in the starting material and four monohydroxylated derivatives, **2b**, **3**, **4**, and **5**, in 15, 14, 6, and 2% yields, respectively, based on the converted product (Scheme I).

The structure of compounds **2–5** was elucidated using ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectra we have monitored the chemical shifts of the C18, C21 and C26, C27 methyl protons (steroid numbering) (Table I). The chemical shift of the C26 and C27 methyl protons in **2a** (δ 1.21) was indicative of a hydroxyl group at C25[10] and that of the C21 protons (δ 1.25) of a hydroxyl group at C20.[11] The structures of the other products were unequivocally established from their ^{13}C NMR spectra.

A complete and self-consistent signal assignment of the ^{13}C NMR spectra of **2a**, **3**, and **4** was made on the basis of their single-frequency off-resonance and the partially relaxed spectra as well as on the lanthanide-induced shifts spectra. The data are collected in Table II.[12] The substituent chemical shifts (SCS) observed for the neighboring carbon atoms as induced by the hydroxyl group substitution confirmed the positions of the hydroxyl group and established their configuration.

Scheme I



In all cases the hydroxyl-substituted carbons appeared as a singlet in the off-resonance spectrum and the SCS for these carbons had the expected order of magnitude (ca. 30.0 ppm for C14 and C17, and ca. 40–45 ppm for the C25). The substitutions at C14 and C17 were determined from the long-range SCS effects on the neighboring carbon atoms. Thus hydroxyl at C14 influences the C8 and C9 positions more than the side-chain carbon atoms, while hydroxyl at C17 has an opposite influence. The α configuration of OH at C17 and C14 in **3** and **4**, respectively, was established from the SCS values for C18. The downfield shifts (ca. 2.5 ppm) observed for C18 are caused by an OH group at the γ-anti position to the methyl group. Similar downfield shifts were observed for C19 in 5α-OH and 9α-OH steroids.[13] These γ effects differ from those caused by an OH group having a gauche relation to a methyl group, where this shift is upfield as examplified by a SCS values of −4.75 ppm for C21 in the 17α-OH derivative **4** (Table II).

Dry Ozonation.[7] The hydrindan derivative **1b** was adsorbed on silica gel and was ozonated at −78 °C for 25 min to give, in addition to the starting material, a mixture (37% conversion) of four compounds, **2b**, **3**, **4**, and **5**, identical with the products of peracetic acid oxidation. The yield of the 25-hydroxy derivative **2b** was 12% of the converted material.

Radical Chlorination with *N,N*-Dichlorourethane.[9] As a starting material we have used the trifluoroacetate **6**, which was irradiated with a sunlamp in benzene solution in the presence of *N,N*-dichlorourethane for 25 min. The total material containing the 25-chloro derivative **7** was converted to the respective 25-hydroxy derivative **8** by

(5) H. H. Inhoffen, G. Quinkert, S. Schütz, D. Kampe, and G. F. Domagk, *Chem. Ber.*, **90**, 664 (1957).
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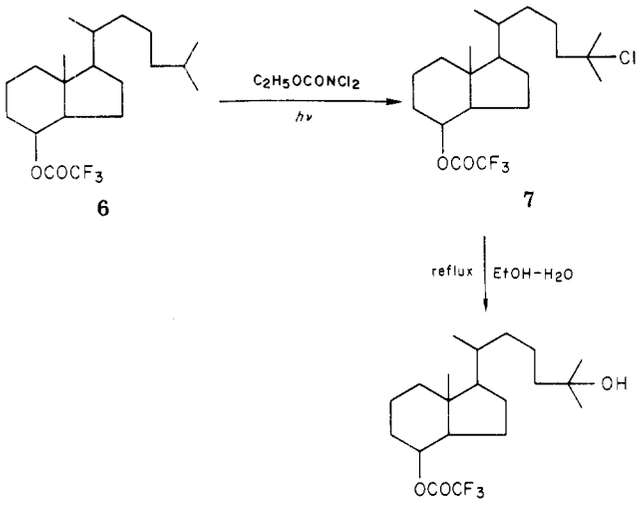
Table II.
^{13}C Chemical Shifts and Substituent Effects Data for Hydrindan 1b and Its Hydroxylated Analogues 2a, 3, and 4[a]

carbon	compd (OH at)				Substituent Effects, $\Delta\delta$,[b] with OH at		
	1b	3 (14α)	4 (17α)	2a (25)	14α	17α	25
8	71.50	73.80	72.20	69.25	2.30	0.70	−0.25
9	30.70	(26.05)	30.40	33.75	−4.65	−0.30	
11	18.05	17.35	17.85	17.55	−0.70	−0.20	
12	40.25	32.55	33.40	40.60	−7.70	−6.85	
13	42.10	34.55	47.60	41.95	3.45	5.50	
14	51.55	82.45	46.05	52.80	30.90	−5.50	
15	22.80	31.35	21.90	22.65	8.55	−0.90	
16	27.15	(25.70)	37.95	27.25	−1.45	10.80	
17	56.75	51.10	86.20	56.90	−5.65	29.45	
18	13.10	15.45	15.85	13.60	2.35	2.75	
20	35.45	35.15	39.20	35.30	0.30	3.75	−0.10
21	18.70	18.70	13.95	18.60	0.00	−4.75	
22	36.10	36.35	32.40	36.40	−0.25	−3.95	0.25
23	23.90	24.10	25.65	20.90	0.20	1.75	−3.05
24	39.65	39.60	39.40	44.50		0.25	4.85
25	28.05	28.05	28.05	70.95			42.90
26	22.60	22.60	22.50	29.20			6.60
27	22.80	22.85	22.80	29.35			6.50

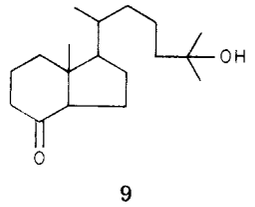
[a] Shifts are given in ppm downfield from internal Me_4Si and are accurate to within 0.1 ppm. The values in parentheses may be interchanged down any column. [b] $\Delta\delta = \delta^{OH} - \delta^{H}$, where δ^{OH} is the shift of the OH substituted C atom and δ^{H} is that of the respective unsubstituted C atom.

Scheme II



heating with 50% ethanol and the derivative was then hydrolyzed with base to the corresponding diol (formed in 21% yield from the trifluoroacetate **6**) (Scheme II).

The diol **2a** was oxidized with pyridinium chlorochromate to the corresponding ketol **9**,[14] which has been



9

recently converted to 25-hydroxyvitamin D_3 by Lythgoe et al.[2]

Experimental Section

^{1}H NMR spectra were recorded on a Bruker WH-90 spectrometer using CCl_4 as a solvent and cyclohexane-d_{12} as an internal lock. The ^{13}C NMR spectra were recorded on the same spectrometer, operating at 22.63 MHz using $CDCl_3$ (ca. 0.05–0.2 M) containing Me_4Si as an internal reference.

All chemical shifts are reported in δ values relative to tetramethylsilane as a standard. The ultraviolet spectra were taken on a Cary 118 spectrophotometer, using ether as a solvent. Mass spectra were recorded on Varian MAT 731 high-resolution mass spectrometer.

Peracetic Acid Oxidation of Acetate[8] **1b.** A solution of acetate **1b** (17.9 g) in ethyl acetate which contained distilled peracetic acid (100 mL, 30%) was irradiated (300 nm). After 17 h, all of the reagent was consumed and another 50 mL of it was added. The irradiation was continued for another 10 h, after which the solution was washed consecutively with sodium bisulfite solution, 10% NaOH, and water. The solution was dried with anhydrous magnesium sulfate and evaporated to dryness. Silica gel chromatography (ether–hexane, 1:1) gave the starting material (7.15 g) and the following products.

Des-*AB*-cholestane-8,25-diol 8-acetate (**2b**, 1.9 g): NMR δ 0.88 (s, 3 H, C18), 1.21 (s, 6 H, C26,27), 2.03 (s, 3 H, OAc), 5.13 (d, 1 H, C-8); MS 324 (M^+), 306 ($M^+ - H_2O$), 59 (C_3H_7O).

Des-*AB*-cholestane-8,14α-diol 8-acetate (**3**, 1.6 g): NMR δ 0.85 (d, J = 6 Hz, 6 H, C26,27), 0.94 (s, 3 H, C18), 2.02 (s, 3 H, OAc); high-resolution MS 324.2676 (M^+, calcd for $C_{20}H_{36}O_3$, 324.2664).

Des-*AB*-cholestane-8,17α-diol 8-acetate (**4**, 0.7 g): NMR δ 0.80 (d, J = 6 Hz, 6 H, C26,27), 0.98 (s, 3 H, C18), 2.04 (s, 3 H, OAc).

Des-*AB*-cholestane-8,20*S*-diol 8-acetate (**5**, 0.3 g): NMR δ 0.86 (d, J = 6 Hz, 6 H, C26,27), 1.04 (s, 3 H, C18), 1.25 (s, 3 H, C21), 2.02 (s, 3 H, OAc).

Dry Ozonation of Acetate[7] **1b.** The title compound (0.5 g) was impregnated on silica gel (50 g) by thorough mixing. The resulting powder was ozonated for 25 min at −78 °C and warmed to room temperature. The silica gel was washed with ethyl acetate at ambient temperature. The solution was evaporated and the residue was chromatographed on silica gel (ether–hexane, 1:1), resulting in starting material **1b** (0.3 g), the derivative **2b** (30 mg), and a mixture consisting of **3**, **4**, and **5**. These products were identified by comparison (TLC, NMR) with the corresponding peracetic acid oxidation products.

Trifluoroacetate 6. Alcohol **1a** (1.34 g) was mixed with trifluoroacetic anhydride (6 mL) for 1 h at 0 °C. The solution was evaporated off under N_2 and then with a high-vacuum pump, resulting in 1.72 g of trifluoroacetate (viscous oil) **6**: NMR δ 0.86 (d, J = 6 Hz, 6 H, C26,27), 0.87 (s, 3 H, C18), 5.33 (b, 1 H, C8).

Chlorination of 6 with *N,N*-Dichlorourethane.[9] Dichlorourethane (366 mg) was added to a solution of trifluoroacetate **6** (400 mg) in dry benzene (40 mL). The mixture was irradiated (sunlamp 4 × 40 W) for 5 h, after which it was evaporated to dryness and the residue was dissolved in 1:1 ethanol–water solution (50 mL) and heated under reflux overnight. The organic material was extracted with dichloromethane, washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness. Chromatography of the residue (silica gel, ether–hexane, 1:1) yielded 50 mg (12%) of viscous oil identified as des-*AB*-cho-

(14) B. Lythgoe, D. A. Rogerts, and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1608 (1977).

lestane-8,25-diol 8-trifluoroacetate (8): NMR δ 1.22 (s, 6 H, C26,27).

Hydrolysis of Trifluoroacetate 8. The title compound (36 mg) was hydrolyzed in KOH–EtOH as described below to give 28 mg of the 8,25-diol **2a**, which was identical with the diol obtained by the basic hydrolysis of acetate **2b**.

Hydrolysis of Acetate 2b. The title compound (1.4 g) was dissolved in a solution of 5% KOH in methanol (200 mL) and stirred overnight at 60 °C. The organic material was extracted with ether and washed with 5% HCl solution, water, and brine. The solution was dried over anhydrous magnesium sulfate and vacuum dried to yield 1.06 g (90%) of the 8,25-diol **2a** as white crystals: mp 89–90 °C (lit.[14] 90–91 °C); NMR 0.92 (s, 3 H, C18), 1.20 (s, 6 H, C26,27); high-resolution MS 282.2565 (M^+, calcd for $C_{18}H_{34}O_2$, 282.2559).

Preparation of Ketol 9. A solution of diol **2b** (0.92 g) in dichloromethane (6 mL) was added at once to a solution of pyridinium chlorochromate (1.1 g) in dichloromethane (10 mL) and mixed for 2 h. The solution was diluted with ether and filtered on a short pad of silica gel. After removal of the solvent, a viscous oil (843 mg, 35%) was obtained identified as the ketol **9**:[14] $[\alpha]_D$ 5.3° ($CHCl_3$); NMR δ 0.63 (s, 3 H, C18), 1.20 (s, 6 H, C26,27); high-resolution MS 280.2382 (M^+, calcd for $C_{18}H_{32}O_2$, 280.2402).

Registry No. **1a**, 33813-99-9; **1b**, 70550-65-1; **2a**, 66774-84-3; **2b**, 70550-66-2; **3**, 70550-67-3; **4**, 70550-68-4; **5**, 70550-69-5; **6**, 70550-70-8; **7**, 70550-71-9; **8**, 70550-72-0; **9**, 70550-73-1.

Synthesis of Novel 3-(Alkylthio)-2-halopyridines and Related Derivatives

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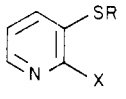
A continuing interest in the chemistry of functionalized pyridines[1,2] has led to a search for synthetic methods capable of generating 2-halopyridines containing either an alkylthio or a trihaloalkylthio group in the 3 position (**1**). Such compounds represent a unique class unknown in pyridine literature. Examples of the type **1**, as well as their oxidation products, could serve as intermediates leading to the preparation of substituted 2-alkoxypyridines, specific examples of which are currently of significant medicinal interest.[3] In principle, such 2-halo derivatives are derivable from the appropriate 3-(alkylthio)pyridine[4,5] via N-oxidation and reaction of the *N*-oxide with $POCl_3$ or an equivalent reagent.[6] However, this method was found to yield an inseparable isomeric mixture of 2- and 6-chloro-3-(alkylthio)pyridines. Because of this, attempts were made to develop a *regioselective* method; we now wish to report in this note on two synthetically distinct approaches which lead exclusively to compounds of the type **1**.

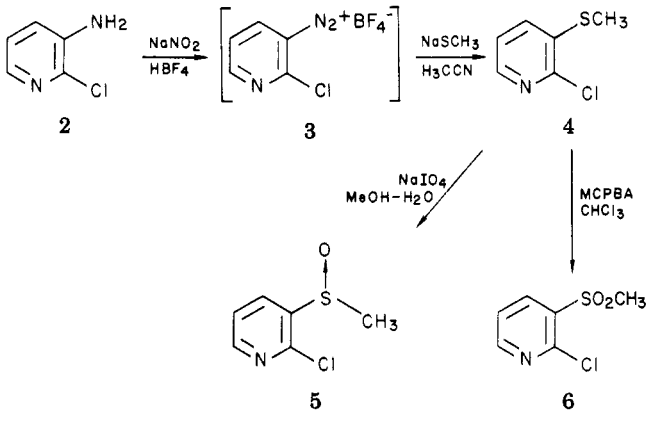


1, R = CH_3, CCl_3, CF_3; X = Br, Cl

Diazotization[7] of 3-amino-2-chloropyridine (**2**) in the presence of 48–50% HBF_4 and subsequent decomposition of the resulting fluoroborate salt **3** in $NaSCH_3$–H_3CCN gave 2-chloro-3-(methylthio)pyridine (**4**) in modest yield (Scheme I). Oxidation of **4** with either $NaIO_4$ or MCPBA provided the sulfoxide **5** and sulfone **6**, respectively.

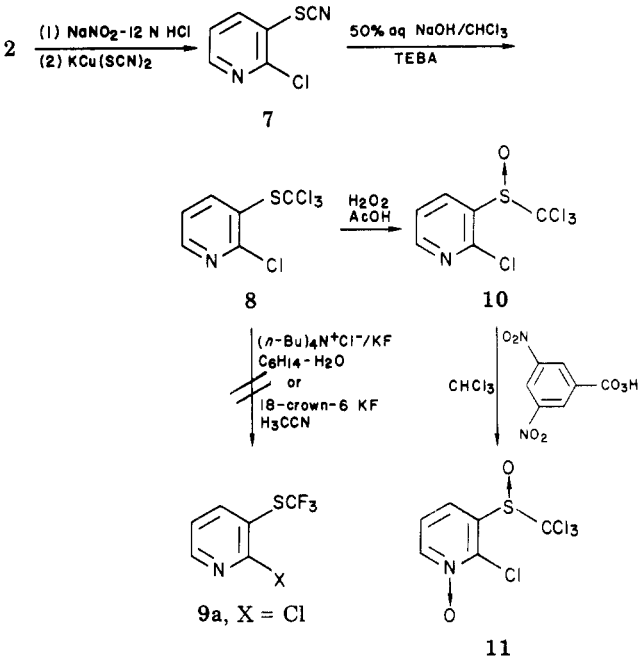
Synthesis of the 3-(trihalomethylthio)pyridines **8** and **9a** was next investigated as outlined in Scheme II. The approach employed was analogous to the reported conversion of aryl thiocyanates to aryl trichloromethyl sulfides[8] followed by an exchange of chloride by fluoride ion utilizing 18-crown-6[9] or phase transfer catalysts.[10] Diazotization of **2** with $NaNO_2$ in concentrated HCl followed by decomposition of the diazonium salt with $KCu(SCN)_2$ gave the thiocyanate **7**. Under phase-transfer

Scheme I



2 3 4 5 6

Scheme II



7 8 10 9a, X = Cl 11

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