50%; mp 155-156 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.1 (s, 3, CH_3), 4.78-5.1 (br, 5, two $NHCH_2$ + one NH), 7.0 (s, 1, imidazole CH), 7.27 (s, 10, two Ph); mass spectrum (70 eV), *m/e* 320 (M^+), 229 ($M^+ - CH_2Ph$).

Anal. Calcd for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.38; H, 6.36; N, 17.27.

1-Benzyl-5-(benzylamino)-4-(benzylcarbamoyl)imidazole (19): from **9b** and benzylamine; colorless needles from EtOH-H_2O (1:1); 53%; mp 140 °C; ^{1}H NMR (Me_2SO-d_6) δ 4.74 (s, 2, NCH_2), 4.82-5.13 (br, 5, two $NHCH_2$ + one NH), 7.11 (s, 1, imidazole CH), 7.28 (s, 15, three Ph); mass spectrum (70 eV), *m/e* 396 (M^+), 305 ($M^+ - CH_2Ph$).

Anal. Calcd for $C_{25}H_{24}N_4O$: C, 75.73; H, 6.10; N, 14.13. Found: C, 75.63; H, 6.10; N, 14.09.

Phenylphosphonic Bis(*N*-benzylamide) (20). A mixture of phenylphosphonic dichloride (0.14 mL, 1 mmol) and dry pyridine (5 mL) was immersed in an oil bath maintained at 70 °C. Benzylamine (1 mL, 9.15 mmol) was introduced through a serum cap, and the reaction mixture was heated at the above temperature, under N_2, for 4.5 h. The reaction mixture was cooled, the precipitated benzylamine hydrochloride was filtered, and the filtrate was evaporated to dryness on a rotary evaporator. The residue was poured over H_2O (50 mL), and the aqueous mixture was extracted with AcOEt (3 × 35 mL). The combined extracts were dried over anhydrous $CaSO_4$ and filtered, and the filtrate was evaporated to obtain a white solid. The solid was further purified by flash chromatography on a silica gel (40-63 μm) column (30 g), employing a mixture of $CHCl_3$-acetone (1:1) (500 mL) as the eluting solvent, at a flow rate of 10 mL/min at 9 psi. Recrystallization from benzene-hexane provided colorless, fluffy needles of **20** (275 mg, 0.82 mmol, 82%), mp 99-100 °C: ^{1}H NMR (Me_2SO-d_6) δ 3.91 (d, *J* = 7.3 Hz, 2, CH_2), 4.04 (d, *J* = 7.4 Hz, 2, CH_2), 4.78-5.20 (br m, 2, two NH, exchangeable with D_2O), 7.15-7.95 (m, 15, three Ph); mass spectrum (70 eV), *m/e* 336 (M^+), 230 ($M^+ - NHCH_2Ph$).

Anal. Calcd for $C_{20}H_{21}N_2PO$: C, 71.40; H, 6.29; N, 8.32. Found: C, 71.05; H, 6.51; N, 8.26.

Acknowledgment. We express our thanks to (a) the donors of the Petroleum Research Fund administered by the American Chemical Society, (b) the National Institutes of Health [Grant No. CA 36154 (to R.S.H.)], and (c) the Sigma Xi, the Scientific Research Society (to B.B.L.) for the support of this research. We are also indebted to Professor Patrick Callery of the School of Pharmacy of the University of Maryland at Baltimore for the mass spectral data.

Registry No. 1, 98832-61-2; 3, 53704-09-9; **3a**, 98832-74-7; 4, 42937-74-6; 5, 98832-62-3; 6, 98876-01-8; **7a**, 98876-02-9; **7b**, 98832-63-4; **8a**, 98832-64-5; **8b**, 98832-65-6; **9a**, 98832-66-7; **9b**, 98832-67-8; **10a**, 98832-68-9; **10b**, 98876-03-0; **11a**, 98832-69-0; **11b**, 98876-04-1; **12a**, 98832-70-3; **12b**, 98832-71-4; 13, 27160-23-2; 14, 54150-80-0; 17, 58091-28-4; 18, 98876-05-2; 19, 98832-73-6; 20, 53721-41-8; trimethyl orthoformate, 149-73-5.

Synthesis of Halogenated Pyridines via the CuCl-Catalyzed Addition of Polyhaloacetonitriles to Olefins

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Halogenated acetonitriles add smoothly to acrolein, methacrolein, and methacrolein dimethyl acetal in the presence of a catalytic amount of CuCl and triphenylphosphine, tri-*n*-butylphosphine, or triethylamine to give halogenated difunctional adducts. The adducts have been cyclized in high yields under acidic conditions to halogenated pyridines.

Historically, very few methods have been described that provide for the multiple introduction of halogens at specific positions on the pyridine ring.[1] Vapor-phase halogenations typically give indiscriminate substitutions,[2a-d] and isolation of specific isomers is often a laborious process. Electrophilic substitution of halogens on the pyridine ring affords some selectivity but frequently requires excessive amounts of Lewis acid catalysts.[3ab] The Schiemann reaction has been used to prepare 2,6-difluoro- and 2,3-difluoropyridine from 6-amino- and 3-amino-2-fluoropyridines.[4] Recently, Martin and co-workers[5a-c] have reported the Cu- and CuCl[6]-catalyzed addition of polychloro aldehydes to acrylonitrile and methacrylonitrile. The resulting adducts were cyclized to afford 2,3-dichloro-5-methylpyridine and 2,3,5-trichloropyridine.[5a] We report an alternative method for the synthesis of halogenated pyridines. We have found that polyhaloacetonitriles add smoothly, under mild conditions, to acrolein and methacrolein in the presence of cuprous chloride and a cocatalyst to afford adducts that readily cyclize to give halogenated pyridines. We have found that this reaction affords a diversity of halogen and mixed-halogen substituents on the pyridine ring and can be attained by the suitable selection of the halogens on acetonitrile. The reaction conditions for the experiments are summarized in Table I.

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(1) For a review of halopyridines synthesis and reactions, see: Boudakian, M. M. In "The Chemistry of Heterocyclic Compounds", Vol. 14. Abramovitch, R. A., Ed. "Pyridine and Its Derivatives", Part II; Wiley: New York, 1974; pp 407-488.

(2) (a) Haszeldine, R. N. *J. Chem. Soc.* **1950**, 1966. (b) Banks, R. E.; Williamson, G. E. *J. Chem. Soc.* **1965**, 815. (c) Talpin, W. H. U.S. Patent 3 420 833, 1969. (d) Den Hertog, H. J.; Combe, W. P.; Kolder, C. R. *Recl. Trav. Chim. Pays-Bas* **1958**, *66*, 77.

(3) (a) Pearson, D. E.; Hargrove, W. W.; Chow, K. T.; Suthers, B. R. *J. Org. Chem.* **1961**, *26*, 789. (b) Johnston, H. U.S. Patent 3 555 032, 1971.

(4) Finger, G. C.; Starr, L. D.; Roe, A.; Link, W. J. *J. Org. Chem.* **1962**, *27*, 3965.

(5) (a) Steiner, E.; Martin, P.; Bellus, D. *Helv. Chem. Acta* **1982**, *65*, 983. (b) Steiner, E.; Martin, P. Eur. Patent Appl. EP 46 735, 1982. (c) Martin, P.; Steiner, E. Eur. Patent Appl. EP 78 243, 1983.

(6) For a review of transition-metal-catalyzed addition of organo halogens to olefins, see: Freidlina, R. Kh.; Chukovskaya, E. C. *Synthesis* **1974**, 477.

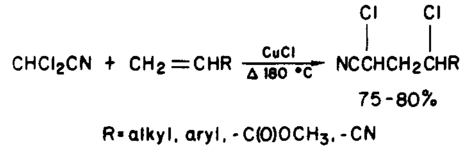
0022-3263/85/1950-5115$01.50/0

Table I. Addition of Polyhalonitriles to Olefins[a]

no.	olefin	polyhalonitrile	catalyst	temp, °C	time, h	% yield of adduct/py
1	methacrolein	$HCCl_2CN$	CuCl·Ph_3P	88	13	40/10
2	methacrolein	$HCCl_2CN$	CuCl·n-Bu_3P	89–99	31	95/...
3	methacrolein	$HCBr_2CN$	CuCl·n-Bu_3P	90	9	.../40
4	methacrolein	HCClFCN	CuCl·n-Bu_3P	90–170	5–10	0/0
5	methacrolein	HCBrFCN	CuCl·n·Bu_3P	90–170	5–10	0/0
6	methacrolein	Br_2CFCN	CuCl·(n-Bu_3P & Et_3N)	110	12	0/30
7	methacrolein	Cl_2CFCN	CuCl·(n-Bu_3P & Et_3N)	110	9	87/...
8	methacrolein dimethyl acetal	$HCCl_2CN$	CuCl·n-Bu_3P	97	15	55/...
9	methacrolein	$HCBr_2CN$	CuCl·n-BuP	105	15	50/...
10	methacrolein	Cl_2CFCN	CuCl·(n-Bu_3P & Et_3N)	110	6	80/...

[a] Solvent propionitrile.

Reactions of Dichloro- and Dibromoacetonitrile. In 1966, Murai and Tsutsumi[7] reported the addition of dichloro- and trichloroacetonitrile to terminal olefins using a wide range of copper(I) salts as catalysts. These reactions were carried out at 180 °C for a period of 18 h:

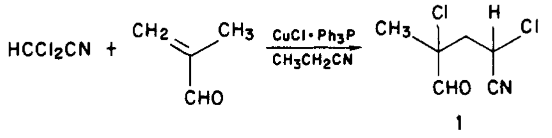


$$CHCl_2CN + CH_2{=}CHR \xrightarrow[\Delta\ 180\ ^\circ C]{CuCl} NC\overset{Cl}{\overset{|}{C}}HCH_2\overset{Cl}{\overset{|}{C}}HR$$

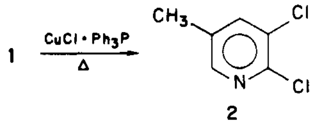
75-80%

R = alkyl, aryl, -C(O)OCH$_3$, -CN

As an extension of this reaction, we felt that the use of methacrolein as the terminal olefin in this addition reaction would allow the synthesis of adducts that could be cyclized to form polyhalogenated pyridines. Subsequently, the CuCl-catalyzed addition of dichloro- and dibromoacetonitrile to methacrolein was investigated. Research quantities of these haloacetonitriles were prepared according to the procedure described by J. W. Wilt.[8] The addition of dichloroacetonitrile to methacrolein was carried out, using CuCl as the catalyst and triphenylphosphine as the cocatalyst in refluxing propionitrile. The reaction was followed by gas chromatography. At a conversion of ~ 40%, the formation of adduct 1 terminated.

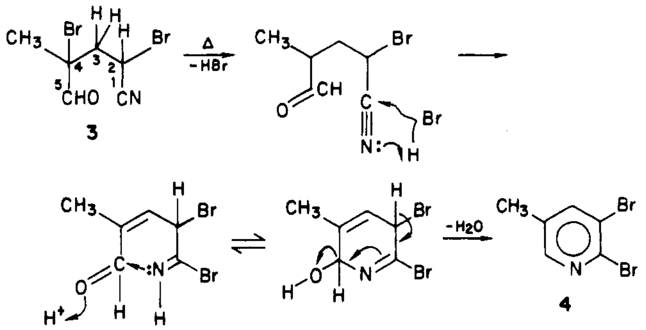


Prolonged heating resulted only in the slow conversion of 1 to 2,3-dichloro-5-methylpyridine (2). The starting materials were recovered unchanged, and a product mixture of adduct 1 and pyridine 2 were isolated with a selectivity of 80%. This abrupt cessation in the conversion suggested a deactivation of catalyst or cocatalyst (Table I, entry 1).



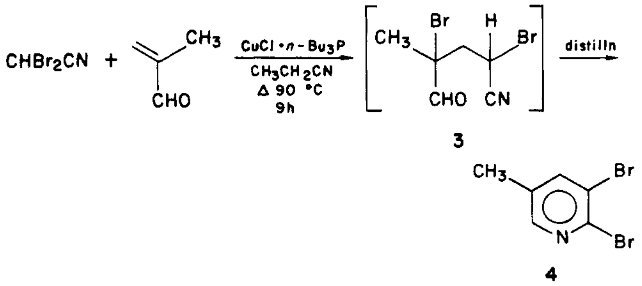
Tri-n-butylphosphine was used in the place of triphenylphosphine. The reaction was carried out as in the previous example by heating a twofold excess of methacrolein in the presence of CuCl·n-Bu$_3$P catalyst (1.0%) in propionitrile. The temperature of the reaction was 89 °C initially; this rose to a final temperature of 99 °C after 31 h at reflux. Heating was maintained until no further conversion was observed. The isolated yield of adduct 1 using tri-n-butylphosphine as a cocatalyst was 95%. By contrast, the reaction of 2,2-dichloropripionaldehyde and acrylontrile under identical conditions resulted in no conversion after refluxing in propionitrile for 48 h. Under optimum conditions, the best results obtained for this reaction were conversions of 40–45% with selectivities of 80–85% at 150 °C.[9] Substantial amounts of the resulting adduct 1 are converted to 2,3-dichloro-5-methylpyridine (2) at these temperatures. Very little, if any, of compound 2 was found from the reaction of dichloroacetonitrile and methacrolein.

Scheme I



The reaction for the direct preparation of 2,3-dichloro-5-methylpyridine (2) from dichloroacetonitrile and methacrolein was carried out with a twofold excess of methacrolein dissolved in propionitrile containing dichloroacetonitrile and a catalytic amount of CuCl and n-Bu$_3$P. The solution was placed in a Carius tube and heated to 130 °C for a period of 6 h. Analysis of the reaction mixture showed a 60% conversion of dichloroacetonitrile and a product mixture containing 2,3-dichloro-5-methylpyridine (2) present in about 40% yield along with 10% of 2,4-dichloro-4-methyl-5-oxopentanenitrile (1).

Similarly, the addition of dibromoacetonitrile to methacrolein was carried out. As in previous examples, 2 equiv of methacrolein was used and the reaction mixture was refluxed for a period of 9 h at 90 °C after which time no further conversion was observed. Distillation of the reaction mixture, however, afforded only 2,3-dibromo-5-methylpyridine (4). No 2,4-dibromo-4-methyl-5-oxopentanenitrile (3) was isolated from the reaction mixture.



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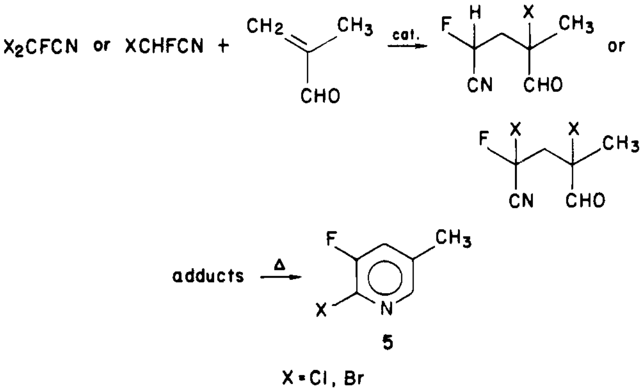
(7) Murai, S.; Tsutsumi, S. *J. Org. Chem.* **1966**, *31*, 3000.
(8) Wilt, J. W. *J. Org. Chem.* **1956**, *21*, 920.
(9) Steiner, E.; Martin, P.; Belluš, D. U.S. Patent 4245098, 1983.

Scheme II

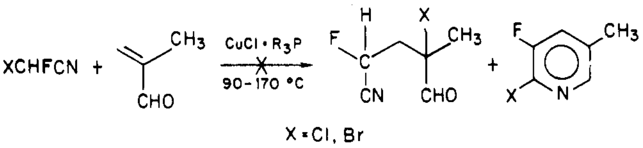


In repeated experiments, similar results were observed with conversions of ~40% of dibromoacetonitrile and 40% yield of 4. It is believed that the bromine on the 4-position of adduct 3 is thermally labile, resulting in a rapid dehydrobromination of this compound at higher temperatures. The HBr, thus formed, can proceed to catalyze the ring-closure reaction to afford pyridine 4 during the course of distillation (Scheme I). No further attempts were made to optimize the formation of 2,3-dibromo-5-methylpyridine or to isolate the intermediate adduct 3 (Table I, entry 3).

Strategy for the Preparation of 3-Fluoro-Substituted Pyridines. The facile addition of polyhaloacetonitriles to acroleins using a copper–phosphine catalyst has suggested the feasibility of selectively introducing a fluorine atom into adducts such as 1 and 3. These new "fluoro" adducts could, if appropriately substituted, be converted into fluorohalopyridines (Scheme II).

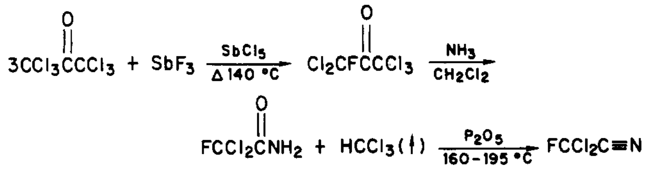
Since the fluorine atom has never been shown to be the migrating species in the transition-metal-catalyzed addition of organo halogens to olefins,[10] the resulting adducts would all contain the fluorine atom on the carbon α to the nitrile group. The predicted products from the cyclization of these adducts would be 2-halo-3-fluoropyridines (5).

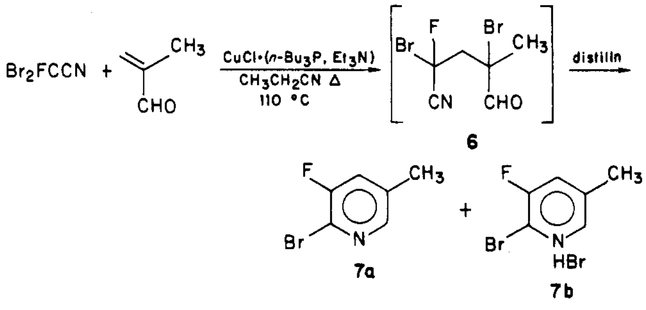
Reactions of Fluorohaloacetonitriles. Our attempts to form adducts from the copper-catalyzed addition of fluorochloro- and fluorobromoacetonitriles were unsuccessful. The addition reactions were carried out under a wide variety of conditions, and neither adducts nor pyridines were detected.



We subsequently decided to examine the addition reactions of dibromofluoroacetonitrile and dichlorofluoroacetonitrile to methacrolein. Both dibromo- and dichlorofluoroacetonitriles were prepared by analogy to methods described by Young and Tarrant.[11] The addition of dibromofluoroacetonitrile to methacrolein was carried out with CuCl as catalyst and tri-n-butylphosphine–triethylamine as cocatalysts (~1%). A twofold excess of methacrolein was present, and propionitrile was used as the solvent. The reaction was heated at 110 °C for a period of 12 h, after which time the solvent was removed in vacuo. The proton NMR of the crude reaction mixture showed the presence of adduct 6 as a mixture of diastereomers. Our attempts to purify 6 by distillation, instead, lead to the isolation of 2-bromo-3-fluoro-5-methylpyridine (7a) and 2-bromo-3-fluoro-5-methylpyridine hydrobromide (7b), which crystallized from the distillate upon standing. The mechanism for this reaction is unclear.

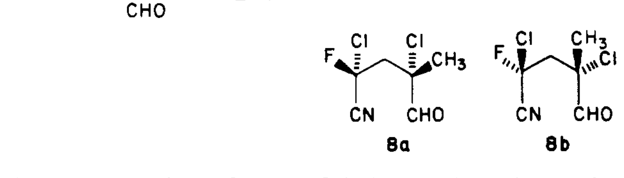
Scheme III





The facile preparation of dichlorofluoroacetonitrile (Scheme III) was readily accomplished from fluoropentachloroacetone prepared by the selective fluorination[12] of hexachloroacetone with a stoichiometric amount of antimony trifluoride in the presence of a catalytic amount of antimony pentachloride. Ammonolysis of fluoropentachloroacetone with anhydrous ammonia gas in methylene chloride at 0 °C readily afforded the chlorofluoroacetamide, which was subsequently dehydrated to the desired product.

The addition of dichlorofluoroacetonitrile to methacrolein was carried out in manner similar to that described for dibromofluoroacetonitrile in the presence of CuCl as catalyst and a combination of tri-n-butylphosphine–triethylamine cocatalysts (~1%). Methacrolein was present in excess, and propionitrile was used as the solvent of the reaction. The resulting solution was heated to 110 °C for a period of 6 h. Removal of the solvent and unreacted starting material under reduced pressure followed by vacuum distillation of the residue afforded diastereomeric mixture of adducts (8a,b). No pyridine (Table I, entry 7) products were detected during the distillation of the adducts. Furthermore, all pyrolytic attempts at ring closure resulted in the formation of tars and multiple reactions products.



Attempts at the reductive dehalogenation of 8 to the 2-fluoro-4-chloro-4-formylvaleronitrile, a compound that would be more readily cyclized to the desired 2-chloro-3-fluoro-5-methylpyridine, resulted in only decomposition of the starting material. Both Zn,H^+ and Ca/Hg,H^+ reductions were tried with similar results.

Additions to Methacrolein Dimethyl Acetal. Initially, we investigated the addition of dibromo- and di-

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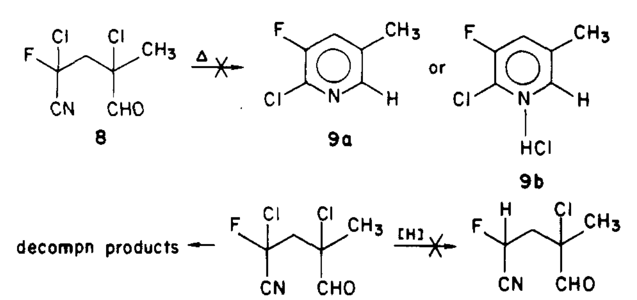
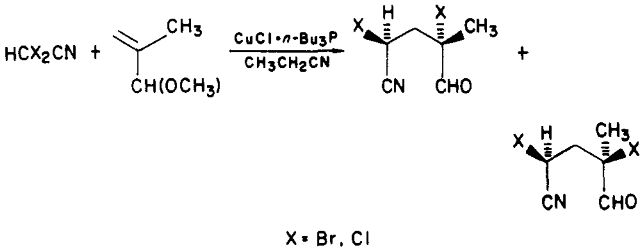
[10] For examples of copper-catalyzed fluorohaloalkane additions, see: Burton, D. J.; Kehoe, L. J. *J. Org. Chem.* **1970**, *35*, 1339.

[11] Young, J. A.; Tarrant, P. *J. Am. Chem. Soc.* **1949**, *71*, 2432.

[12] Miller, C. B.; Woolf, C. U.S. Patent 2 807 646, 1975.



chloroacetonitrile to methacrolein dimethyl acetal. These additions were carried out with an excess of methacrolein dimethyl acetal in propionitrile with CuCl·n-Bu$_3$P as catalyst. The resulting adducts were isolated as mixtures of diastereomers, after the removal of solvent and unreacted starting materials, in yields of 75–85% at conversions of 50–60%. It should be noted that no effort was made to optimize the reaction conditions for these examples (Table I, entries 8 and 9).



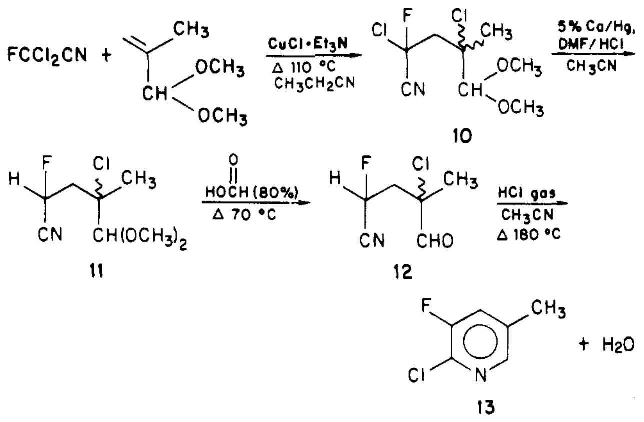
The stability of the adduct, 2,4-dibromo-4-methyl-5,5-dimethoxypentanenitrile (obtained from the addition of dibromoacetonitrile and methacrolein dimethyl acetal), was found to be substantially improved over that of the adduct obtained from the reaction of dibromoacetonitrile and methacrolein itself, which could not be isolated but was converted to 2,3-dibromo-5-methylpyridine upon distillation.

Synthesis of 2-Chloro-3-fluoro-5-methylpyridine. The addition of dichlorofluoroacetonitrile to methacrolein dimethyl acetal was considered to be an alternative route to the preparation of 2-chloro-3-fluoro-5-methylpyridine (Scheme IV). Adducts obtained from this addition would be more stable to reductive conditions. Thus, 2,4-dichloro-2-fluoro-4-methyl-5,5-dimethoxypentanenitrile (**10**) was obtained as a mixture diastereomers in 87% yield. The reduction of **10** with 5% Cd/Hg afforded **11**, which was hydrolyzed with formic acid to afford **12** in 65% yield. Cyclization of **12** with HCl in acetonitrile at 180 °C gave 2-chloro-3-fluoro-5-methylpyridine.

Experimental Section

Preparation of 2,4-Dichloro-4-methyl-5-oxopentanenitrile (1). A solution of dichloroacetonitrile (11 g, 0.1 mol) and methacrolein (14.0 g, 0.2 mol) in 50 mL of propionitrile containing 100 mg of CuCl and 200 mL of tri-n-butylphosphine was heated to reflux in a 250-mL round-bottomed flask. The reaction was refluxed under N_2 for a period of 18 h during which time the temperature rose from 85 to 95 °C. After cooling to room temperature, the solvent and unreacted starting materials were removed in vacuo, and the residue was distilled in a Kugelrohr apparatus at 100 °C (5 mmHg) to afford 15 g (80%) of 2,4-dichloro-4-methyl-5-oxopentanenitrile isolated as a 1:1 mixture of diastereomers containing traces of 2,3-dichloro-5-methylpyridine. Redistillation afforded 14.5 g of essentially pure 2,4-dichloro-4-methyl-5-oxopentanenitrile as 1:1 mixture of diastereomers: bp 90 °C (0.5 mmHg) [lit.[9] bp 76–77 °C (0.1 mmHg)]; ^{1}H NMR (acetone-d_6, Me$_4$Si) δ 1.78 (s, 3 H, CH$_3$), 2.3–3.1 (m, 2 H, CH$_2$), 4.75 (5, 1 H, CHCl), 9.5 (s, 1 H, CHO); IR (NaCl, neat) 1750, 2250 cm^{-1}. Anal. Calcd for $C_7H_9Cl_2NO$: C, 43.22; H, 4.67; N, 7.21. Found: C, 43.41; H, 4.65; N, 7.20.

Scheme IV



Preparation of 2,3-Dichloro-5-methylpyridine (2). Direct Method. A solution of dichloroacetonitrile (11.0 g, 0.1 mol) and methacrolein (14 g, 0.2 mol) in 50 mL of propionitrile containing 200 mg of CuCl and 200 mg of tri-n-butylphosphine was placed in a Carius tube and heated to 130 °C for a period of 6 h. Upon completion, the reaction was cooled to room temperature, and the solvent and unreacted starting materials were removed in vacuo. The residue was distilled through a Kugelrohr apparatus at 100–120 °C (5 mmHg) to afford a pale yellow liquid that slowly crystallized upon standing. The white crystals were washed with cold hexane and dried to afford 2,3-dichloro-5-methylpyridine: 10.8 g (40%); mp 42–45 sC (lit.[9] mp 43–45 °C); ^{1}H NMR (acetone-d_6) δ 2.34 (s, 3 H, CH$_3$), 7.59 (d, 1 H, py C$_4$-H), 8.13 (d, 1 H, py C$_6$H). Evaporation of the hexane wash afforded 2,4-dichloro-5-methyl-5-oxopentanenitrile, 2.0 g (~10%).

Preparation of 2,3-Dibromo-5-methylpyridine (4). A solution of dibromoacetonitrile (19.0 g, 0.1 mol) and methacrolein (14.0 g, 0.2 mol) in 50 mL of acetonitrile containing 50 mg of CuCl and 150 mg of tri-n-butylphosphine as catalyst was heated to reflux at 90 °C for 14.5 h after which time the solvent and unreacted starting materials were removed in vacuo. The residue was distilled on a Kugelrohr apparatus to afford 2,3-dibromo-5-methylpyridine (14.0 g, 40%) as a yellow oil that crystallized upon standing. The crystals were washed with cold hexane and dried: mp 53–55 °C; ^{1}H NMR (acetone-d_6) δ 2.28 (s, 3 H, CH$_3$), 7.65 (d, 1 H, py 4-H), 8.15 (d, 1 H, py 6-H). Anal. Calcd for $C_6H_5Br_2N$: C, 28.72; H, 2.01; N, 5.58. Found: C, 29.00; H, 2.00; N, 5.58.

Attempted Preparation of 2-Fluoro-4-chloro-4-formylvaleronitrile. To a 200-mL Carius tube was added chlorofluoroacetonitrile (9.5 g, 0.10 mol), methacrolein (14.0 g, 0.20 mol), and 50 mL of acetonitrile containing 100 mg of CuCl, 50 μL of tri-n-butylphosphine, and 50 μL of triethylamine as catalyst. The solution was heated to 130 °C for a period of 6 h after which time it was cooled to room temperature. Analysis of the reaction mixture showed the presence of multiple reaction products, in small amounts, along with unconverted starting materials. Similar results were observed when bromofluoroacetonitrile and methacrolein were reacted.

Preparation of 2,4-Dichloro-2-fluoro-4-methyl-5,5-dimethoxypentanenitrile (10). A 200-mL Carius tube was charged with methacrolein (15.0 g, 0.13 mol), dimethyl acetal, dichlorofluoroacetonitrile (11.0 g, 0.10 mol), and 50 mL of propionitrile containing 100 mg of CuCl and 40 μL of triethylamine. The resulting solution was heated to 110 °C for a period of 6 h. The reaction was then cooled to room temperature, the solvent and unreacted starting materials were removed in vacuo, and the residue was distilled in a Kugelrohr apparatus at 130 °C (2 mmHg) to afford 12.1 g of 2,4-dichloro-2-fluoro-4-methyl-5,5-dimethoxypentanenitrile as a mixture of diastereomers in 87% yield based on the dichlorofluoroacetonitrile charged: bp 59–61 °C (0.4 mmHg); ^{1}H NMR (acetone-d_6) δ 1.63–1.80 (m, 3 H, CH$_3$), 2.75–3.30 (m, 2 H, CH$_2$), 3.50–3.70 (m, 6 H, C(OCH$_3$)$_2$), 4.30–4.45 (m, 1 H, CH(O)$_2$); IR (NaCl, neat) 2258, 1110, 1080 cm^{-1}. Anal. Calcd for $C_8H_{12}Cl_2FNO_2$: C, 39.36; H, 4.96; N, 5.74. Found: C, 39.65; H, 5.12; N, 5.60.

Preparation of 2-Fluoro-4-chloro-4-methyl-5,5-dimethoxypentanenitrile (11). Cadmium metal (5.0 g, 0.045 mol) dissolved in 95 g of mercury and 100 mL of acetonitrile were added to a 250-mL round-bottomed flask. The mixture was brought to reflux and 2,4-dichloro-2-fluoro-4-methyl-5,5-dimethoxypentanenitrile (10.8 g, 0.04 mol) in 5 mL of acetonitrile containing 0.05 mol of dimethylformamide–hydrochloride salt was added dropwise to the reaction mixture. After completion of addition, reflux was maintained for an additional 5 h during which time a precipitate of cadmium chloride formed. The salts and mercury were then removed by filtration; the filtrate was added to 250 mL of methylene chloride and extracted with 3 × 100 mL portions of water. The solvent was removed in vacuo and the residue distilled on a spinning-band column to afford 2-fluoro-4-chloro-4-methyl-5,5-dimethoxypentanenitrile [8.0 g (94%); bp 50–52 °C (0.3 mmHg)] as a mixture of diastereomers: ^{1}H NMR (acetone-d_6) δ 1.5–1.75 (m, 3 H, CH_3), 2.60 (dm, 2 H, CH_2, $J_{HF} = 20.76$ Hz), 3.58 (m, 6 H, $C(OCH_3)_2$), 4.38 (m, 1 H, $CH(O)_2$), 5.80 (dt, 1 H, CHF, $J_{HF} = 46.6$ Hz); IR (NaCl, neat) 2260, 1070 cm^{-1}. Anal. Calcd for $C_8H_{13}ClFNO_2$: C, 45.83; H,6.25; N, 6.68. Found: C, 45.0; H, 6.25; N, 6.58.

Preparation of 2-Fluoro-4-chloro-4-formylvaleronitrile (12). To a 50-mL round-bottomed flask was added 2-fluoro-4-chloro-4-methyl-5,5-dimethoxypentanenitrile (40 g, 0.2 mol), 15 mL of 80% formic acid, and 5 mL of methylene chloride. The solution was heated to 70 °C for a period of 45 min and cooled to room temperature. Methylene chloride (50 mL) was added to the reaction mixture with 2 × 50 mL portions of water and a 2 × 50 mL portion of saturated potassium carbonate. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was placed on a spinning-band column and distilled to afford 5.0 g of 2-fluoro-4-chloro-4-formylvaleronitrile [65%; bp 62 °C (0.55 mmHg)] as a mixture of diastereomers: ^{1}H NMR (acetone-d_6) δ 1.75 (s, 3 H, CH_3), 2.50–3.10 (dm, 2 H, CH_2), 5.80 (dm, 1 H, HCF), 9.40–9.60 (m, 1 H, CHO); IR (NaCl, heat) 1750, 2250 cm^{-1}.

Preparation of 2-Chloro-3-fluoro-5-methylpyridine (13). 2-Fluoro-4-chloro-4-formylvaleronitrile (1.92 g) was placed in a 50-mL Carius tube with 10 mL of acetonitrile. Dry HCl gas was passed into the solution for 10 s. The reaction mixture was then heated at 180 °C for 20 min. The acetonitrile was removed under reduced pressure, dissolved in 5 mL of methylene chloride, and eluted on a silica gel column (230–499 mesh, 4 cm × 20 cm). The first fraction obtained contained the desired 2-chloro-3-fluoro-5-methylpyridine. Removal of the solvent in vacuo afforded 700 mg (44%) of the product: ^{1}H NMR (acetone-d_6) δ 2.35 (s, 3 H, CH_3), 7.50 (dd, 1 H, py 4H), 8.07 (br s, 6 H); IR (NaCl, neat) 1450, 1408, 1215, 1085, 880, 720, 711 cm^{-1}; Chemical ionization MS CH_4, m/e (relative abundance), MH^+, m/e 146 (100%), MH + 2, m/e 148 (35%).

Preparation of 2,4-Dichloro-4-methyl-5,5-dimethoxypentanenitrile. To a 100-mL round-bottomed flask was added 15 g of methacrolein dimethyl acetal (0.13 mol), 11 g of dichloroacetonitrile (0.10 mol), and 40 mL of propionitrile with 0.5 g of CuCl and 0.5 g of tri-*n*-butylphosphine. The reaction was heated to reflux (97 °C) for a period of 15 h. At this time, the reaction was cooled to room temperature. Analysis by gas chromatography showed approximately a 50–55% conversion of dichloroacetonitrile by area percent. The solvents and unreacted starting materials were removed in vacuo, and the residue was distilled on a Kugelrohr apparatus to afford 4-methyl-5,5-dimethoxypentanenitrile as a mixture of diastereomers: bp 78–79 °C (1.10 mmHg); ^{1}H NMR (acetone-d_6) δ 1.56 (s, 3 H, CH_3), 2.30–2.95 (m, 2 H, CH_2), 3.45–3.65 (m, 6 H, $(OCH_3)_2$), 4.40 (s, 1 H, CH), 5.05–5.30 (m, 1 H, CH); IR (neat, NaCl) 2250, 1450, 1185, 1105, 1080 cm^{-1}. Anal. Calcd for $C_8H_{13}Cl_2NO_2$: C, 42.49; H, 5.79; N, 6.20. Found: C, 42.5; H, 5.83; N, 6.15.

Preparation of 2,4-Dibromo-4-methyl-5,5-dimethoxypentanenitrile. To a 100-mL round-bottomed flask containing 40 mL of propionitrile, 1.0 g of CuCl, and 1.0 g of tri-*n*-butylphosphine were added 21.5 g of methacrolein dimethylacetal (0.19 mol) and 19.0 g of dibromoacetonitrile (0.10 mol). The mixture was heated to reflux for a period of 15 h (105 °C). Upon completion, the unreacted starting materials and solvent were removed in vacuo. The residue was placed on a Kugelrohr apparatus and distilled at 160 °C (2.5 mmHg) to afford diastereomeric 2,4-dibromo-4-methyl-5,5-dimethoxypentanenitrile as a deep brown oil: bp 99 °C (0.5 mmHg); ^{1}H NMR (acetone-d_6) δ 1.81, 1.85 (s, 3 H, CH_3), 2.70–2.85 (m, 2 H, CH_2), 3.60 (m, 6 H, $(OCH_3)_2$), 4.45, 4.50 (1 H, C(Cl)H), 4.85–52 (m, 1 H, BrCH); IR (NaCl, neat) 2255, 1500, 1105, 1075 cm^{-1}. Anal. Calcd for $C_9H_{13}BrNO_2$: C, 30.5; H, 4.16; N, 4.45. Found: C, 30.6; H, 4.26; N, 4.44.

Preparation of 2,4-Dibromo-2-fluoro-4-formylvaleronitrile and Its Conversion to 2-Bromo-3-fluoro-5-methylpyridine (7a) and 2-Bromo-3-fluoro-5-methylpyridine Hydrobromide (7b). Dibromofluoroacetonitrile (5.0 g, 0.025 mol) and 3.5 g (0.05 mol) of methacrolein were dissolved in 50 mL of propionitrile containing 50 mg of CuCl, 50 μL of tri-*n*-butylphosphine, and 50 μL of triethylamine. This solution was placed in a Carius tube and heated at 110 °C for a period of 12 h. Upon completion, the solvent and unreacted starting material were removed under reduced pressure. A ^{1}H NMR spectrum of material showed the presence of diastereomeric 2,4-dibromo-2-fluoro-4-formylvaleronitrile along with a trace amount of 2-bromo-3-fluoro-5-methylpyridine: ^{1}H NMR (acetone-d_6) δ 1.95, 2.0 (2, 3 H, CH_3), 3.2–3.65 (m, 2 H, 4-CH_2), 9.20–9.35 (d, 1 H, CHO). Distillation of this residue through a Kugelrohr apparatus at 120 °C (3 mmHg) afforded only a mixture of pyridines. The distillate, which contained a precipitate, was taken up in hot hexane and filtered to remove the precipitate. This precipitate was dried and purified by sublimation [50–80 °C (0.5 mmHg)] to afford 0.795 g (11.7% yield) of 2-bromo-3-fluoro-5-methylpyridine hydrobromide: mp 198–203 °C (sub.); ^{1}H NMR (acetone-d_6/D_2O, 1:1) δ 2.45 (s, 3 H, CH_3), 8.75 (dm, 1 H, py 4H, $J_{HF} = 9.4$ Hz), 8.15 (br s, 1 H, py 6H). Removal of the hexane in vacuo afforded a colorless oil that solidified on standing. Sublimation of this material (30 °C at 0.3 mmHg) gave 0.95 g (20%) of 2-bromo-3-fluoro-5-methylpyridine: mp 32–33 °C; ^{1}H NMR (acetone-d_6) δ 2.35 (s, 3 H, CH_3), 7.50 (dm, 1 H, py 4H, $J_{HF} = 9.3$ Hz), 8.10 (br, 1 H, py 6H). Anal. Calcd for $C_6H_6Br_2FN$: C, 26.59; H, 2.23; N, 5.17. Found: C, 26.30; H, 2.54; N, 5.09. Anal. Calcd for C_6H_5BrFN: C, 37.92; H, 2.65; N, 7.37. Found: C, 37.24; H, 2.85; N, 6.98.