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.

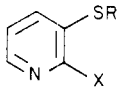
## Synthesis of Novel 3-(Alkylthio)-2-halopyridines and Related Derivatives

Gerald S. Ponticello,* Richard D. Hartman, William C. Lumma, Jr., and John J. Baldwin*

*Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486*

*Received February 8, 1979*

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**.

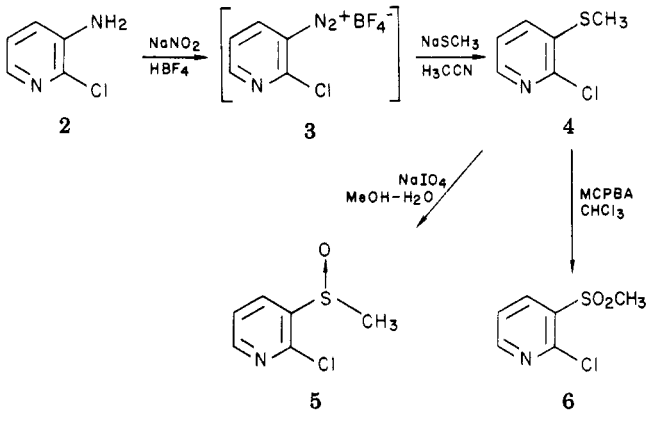


1, R = $CH_3$, $CCl_3$, $CF_3$; X = Br, Cl

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.

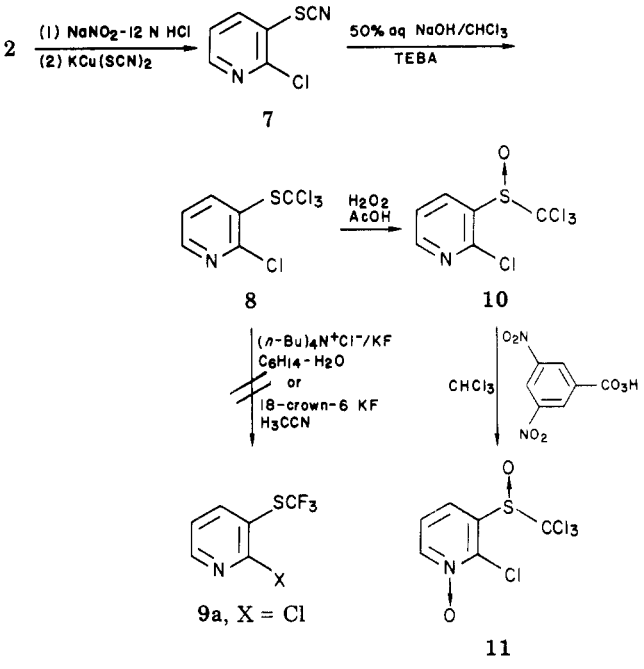
Synthesis of the 3-(trihalomethylthio)pyridines **8** and **9a** was next investigated as outlined in Scheme II. The approach employed was analogous to the reported conversion of aryl thiocyanates to aryl trichloromethyl sulfides[8] followed by an exchange of chloride by fluoride ion utilizing 18-crown-6[9] 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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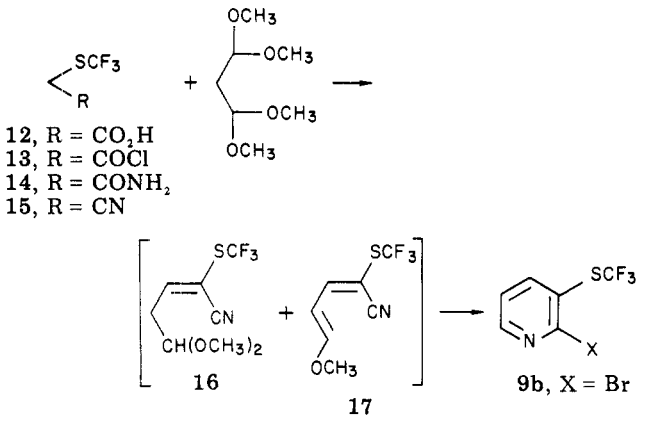
**Scheme III**




conditions, **7** reacted with a mixture of 50% aqueous $NaOH-CHCl_3$ containing triethylbenzylammonium chloride (TEBA)[8] to yield **8**. However, compound **8** proved to be inert to fluoride ion but was susceptible to $H_2O_2$–AcOH oxidation to yield sulfoxide **10**.

In contrast to **4**, compound **10** was inert to *m*-chloroperbenzoic acid but was slowly oxidized to the *N*-oxide **11** by 3,5-dinitroperbenzoic acid.[11] The structure of **11** was assigned on the basis of IR, $^1H$ NMR, and mass spectra. The IR spectra of **10** and **11** were similar except for a strong broad absorption band observed at 1265 $cm^{-1}$ for the latter, attributed to the *N*-oxide function. The $^1H$ NMR spectra of **11** showed respectively 0.56 and 0.17 ppm upfield shifts for $H_4$ and $H_6$ relative to the same protons of **10** which, according to Abramovitch,[12] are characteristic for the introduction of an *N*-oxide. In addition, the observed upfield shift of $H_4$ of **11** relative to $H_4$ of **10** was inconsistent with sulfone formation, since an opposite downfield shift for $H_4$ was observed when sulfone **6** was compared with sulfoxide **5** (see Experimental Section). Finally, the high-resolution mass spectrum of **11** exhibited a molecular ion at *m/e* 292.8643 ($C_6H_3Cl_4NO_2S$) and a prevalent fragment ion for loss of $Cl_3CO$ which is characteristic of the expected Pummerer sulfoxide rearrangement product.

This stability of **8** to halogen exchange prompted a search for an alternate way to generate **9**. A method reported by Bryson and co-workers[13] for the synthesis of certain 3-substituted-2-bromopyridines offered a potentially attractive alternative. As described in Scheme III, the prerequisite (trifluoromethylthio)acetic acid (**12**)[14] was converted to (trifluoromethylthio)acetyl chloride (**13**)[15,16] on treatment with a slight excess of $SOCl_2$.[17] Subsequently, **13** was converted to the amide **14** on reaction with cold, concentrated $NH_4OH$. Dehydration of **14** with $P_2O_5$ resulted in high yield of the nitrile **15**,[15] which on condensation with 1,1,3,3-tetramethoxypropane in the presence of $Ac_2O$ containing a catalytic amount of $ZnCl_2$[13] gave a mixture of the $\beta,\gamma$-unsaturated aldehyde equivalents, **16** and **17**. Finally, cyclization with HBr–AcOH gave the novel 2-bromo-3-(trifluoromethylthio)pyridine **9b**.

In summary, three distinct routes have been developed for the synthesis of pyridines of the type **1**. Two of these proceeded by diazotization of 3-amino-2-chloropyridine (**2**) to provide either 2-chloro-3-(methylthio)pyridine (**4**) or the versatile intermediate 2-chloro-3-thiocyanopyridine (**7**) which was converted to the novel trichloromethylthio derivative **8**. The third approach involved pyridine ring construction from (trifluoromethylthio)acetonitrile (**15**); the success of this method significantly extends the utility of the tetramethoxypropane pyridine synthesis.

## Experimental Section

Infrared spectra were obtained on Perkin-Elmer Model 137 and 257 spectrophotometers. NMR spectra were determined in the indicated solvent on a Varian T-60 spectrometer using tetramethylsilane as an internal standard for proton spectra and fluorotrichloromethane for $^{19}F$ spectra. Mass spectra were taken on an AEI MS-902 high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 500 mA. The data were processed by a DS50 data acquisition system. Melting points were determined on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Liquids were distilled by short-path distillation, and boiling points are uncorrected. Silica gel 60 (E. Merck, Darmstadt) and aluminum oxide 90 (E. Merck, Darmstadt) were used for column chromatography. Solutions were dried over $Na_2SO_4$ and concentrated to dryness using a Buchi rotary evaporator under water aspirator pressure (20 mm).

**2-Chloro-3-(methylthio)pyridine (4).** To a solution of **2** (12.2 g, 0.1 mol) in 48–50% $HBF_4$ (40 mL) and 95% EtOH (75 mL) cooled in an ice bath was added dropwise a solution of $NaNO_2$ (6.9 g, 0.1 mol) in $H_2O$ (20 mL) while maintaining the temperature below 5 °C. After completion of the addition, $Et_2O$ (100 mL) was added, and the fluoroborate salt **3** was removed by filtration and washed with $Et_2O$. The damp solid was then used directly in the next step.

A mixture of **3** (0.1 mol) and $H_3CCN$ (200 mL) was stirred in an ice bath while $NaSCH_3$ (4.2 g, 0.06 mol) was added portionwise.[18] After each addition, a vigorous evolution of $N_2$ was observed, and on completion of the addition the mixture was stirred at 25 °C overnight. The suspension was then filtered, and the solution was concentrated. The residue was treated with $CHCl_3$, filtered, and concentrated to an oil which distilled at 96–7 °C (0.6 mm) to yield 2.2 g (23%) of **4**. An analytical sample was prepared by crystallization from $CH_2Cl_2-C_6H_{14}$: mp 32–3 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 2.5 (3 H, s), 7.3 (2 H, m), and 8.05 (1 H, dd, $J$ = 2 and 5 Hz).

Anal. Calcd for $C_6H_6ClNS$: C, 45.14; H, 3.78; N, 8.77. Found: C, 44.79; H, 3.67; N, 9.04.

**2-Chloro-3-(methylsulfinyl)pyridine (5).** A solution of **4** (1.2 g, 0.007 mol) in $CH_3OH$ (150 mL) was added dropwise to a cold (0–4 °C) solution of $NaIO_4$ (1.6 g, 0.0074 mol) in $H_2O$ (25 mL). After the addition, the mixture was allowed to stir at 25 °C for 5 days with the periodic addition of $NaIO_4$ (3 g) in $H_2O$ (75 mL). The resulting suspension was filtered. The filtrate was concentrated and extracted twice with $CH_2Cl_2$. The organic extract was dried, filtered, and concentrated. An analytical sample of **5** was prepared by sublimation at 55 °C (0.2 mm): mp 67–9 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 2.85 (3 H, s), 7.5 (1 H, dd, $J$ = 4 and 6 Hz), 8.24 (1 H, dd, J = 2 and 6 Hz), and 8.47 (1 H, dd, $J$ = 2 and 4 Hz; IR (Nujol) 1030 $cm^{-1}$.

Anal. Calcd for $C_6H_6ClNOS$: C, 41.03; H, 3.44; N, 7.98. Found: C, 41.15; H, 3.56; N, 8.32.

**2-Chloro-3-(methylsulfonyl)pyridine (6).** A solution of MCPBA (85% pure, 1.9 g, 0.009 mol) in $CHCl_3$ (25 mL) was added dropwise at 25 °C to a solution of **4** (0.7 g, 0.0044 mol) in $CHCl_3$ (25 mL). After being stirred at 25 °C for 18 h, the solution was poured into a saturated solution of $NaHCO_3$, separated, and

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(15) Harris, J. F. *J. Org. Chem.* **1972** *37*, 1340. Since trifluoromethylsulfonyl chloride is no longer commercially available, this route to **13** was not undertaken.

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(17) Large excesses of $SOCl_2$ were avoided since **13** tended to co-distill with it.

(18) When the fluoroborate salt **3** was added to a suspension of $NaSCH_3$ in $H_3CCN$, a 19% yield of **4** was obtained.

extracted twice with $CHCl_3$. The organic layer was dried, filtered, and concentrated to yield 0.82 g (98%) of **6**; an analytical sample was prepared by crystallization from $CH_2Cl_2$–$C_6H_{14}$: mp 106–8 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 3.35 (3 **H**, s), 7.50 (1 H, dd, $J$ = 4 and 6 Hz), 8.47 (1 H, dd, $J$ = 2 and 6 Hz), and 8.63 (1 H, dd, $J$ = 2 and 4 Hz); IR (Nujol) 1300 and 1160 $cm^{-1}$.

Anal. Calcd for $C_6H_6ClNO_2S$: C, 37.60; H, 3.16; N, 7.31. Found: C, 37.88; H, 3.10; N, 7.36.

**2-Chloro-3-thiocyanopyridine (7).** To a solution of **2** (25.7 g, 0.2 mol) in concentrated HCl (350 mL) was added dropwise at −10 to 0 °C a solution of $NaNO_2$ (17 g, 0.2 mol) in $H_2O$ (65 mL). After complete addition, the mixture was stirred an additional 0.5 h and then added with stirring to a solution of KCu $(SCN)_2$ (24.4 g, 0.11 mol) and KSCN (120 g) in $H_2O$ (2.5 L). After the evolution of $N_2$ ceased, the dark-colored solution was filtered through super cel, and the pad was washed well with $Et_2O$. After separating the $Et_2O$ layer, the aqueous layer was extracted twice with $Et_2O$. The combined $Et_2O$ extracts were washed with $H_2O$, saturated NaCl, and saturated $Na_2CO_3$, dried, filtered, and concentrated. The residue was sublimed at 80 °C (0.2 mm) to yield 25.6 g (75%) of **7**: mp 79–80 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 7.43 (1 H, dd, $J$ = 4 and 8 Hz), 8.07 (1 H, dd, $J$ = 5 and 8 Hz), and 8.43 (1 H, dd, $J$ = 2 and 4 Hz); IR (Nujol) 2175 $cm^{-1}$.

Anal. Calcd for $C_6H_3ClN_2S$: C, 42.24; H, 1.77; N, 16.42. Found: C, 42.35; H, 1.80; N, 16.30.

**2-Chloro-3-(trichloromethylthio)pyridine (8).** To a solution of **7** (3.42 g, 0.02 mol) and TEBA (0.5 g) in $CHCl_3$ (76 g, 0.6 mol) was added dropwise a solution of 50% aqueous NaOH (40 mL). After complete addition, the black solution was stirred for 1 h at 25 °C and then filtered through super cel. The layers were separated, and the aqueous layer was further extracted twice with $CHCl_3$. The organic phases were dried, filtered, and concentrated. The residue was placed on a column of dry silica gel and eluted with $CHCl_3$ to yield, after evaporation of the solvent, 5.3 g (59%) of **8**: bp 93–5 °C (0.15 mm); $^1H$ NMR ($CDCl_3$) $\delta$ 7.37 (1 H, dd, $J$ = 4 and 8 Hz), 8.3 (1 H, dd, $J$ = 2 and 8 Hz), and 8.53 (1 H, dd, $J$ = 2 and 4 Hz).

Anal. Calcd for $C_6H_3Cl_4NS$: C, 27.40; H, 1.15; N, 5.33. Found: C, 27.69; H, 1.30; N, 5.35.

**2-Chloro-3-(trichloromethylsulfinyl)pyridine (10).** To a solution of **8** (10.6 g, 0.04 mol) in AcOH (50 mL) was added aqueous $H_2O_2$ (30%, 12 mL). After the solution was stirred for 48 h at 25 °C, additional $H_2O_2$ (30%, 1 mL) was added, and the mixture was stirred at 25 °C for 24 h. The mixture was then concentrated at 40 °C. The residual orange oil was partitioned between $H_2O$–$CHCl_3$ and separated, and the aqueous layer was further extracted with $CHCl_3$ (2×). The organic phases were dried, filtered, and concentrated to yield 9.7 g (82%) of **10**. An analytical sample was crystallized from $C_6H_{14}$: mp 86–87 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 7.50 (1 H, dd, $J$ = 5 and 8 Hz), 8.41 (1 H, dd, $J$ = 2 and 8 Hz), and 8.64 (1 H, dd, $J$ = 2 and 5 Hz); IR ($CHCl_3$) 1095 $cm^{-1}$.

Anal. Calcd for $C_6H_3Cl_4NOS$: C, 25.83; H, 1.08; N, 5.02; Cl, 50.84. Found: C, 26.24; H, 0.99; N, 5.41; Cl, 50.52.

**2-Chloro-3-(trichloromethylsulfinyl)pyridine 1-Oxide (11).** 3,5-Dinitroperbenzoic acid was prepared according to the procedure of Rastetter[11] from 3,5-dinitrobenzoic acid (16.4 g, 0.078 mol) and 90% $H_2O_2$ (10 mL) in methanesulfonic acid (42 g). The mixture was stirred for 3 h at 53 °C after an initial exotherm. The workup as described[11] yielded 14 g of a light yellow solid, mp 182–90 °C dec (lit.[11] mp 113–15 °C then 195–200 °C). Iodometric titration indicated 106.2% of theoretical active oxygen.

A slurry of **10** (0.7 g, 0.0025 mol) and the above peracid (0.57 g, 0.0025 mol) in $CHCl_3$ (10 mL) was stirred for 2 days at 25 °C and then refluxed for 2 h. The mixture was cooled, diluted with four volumes of $CHCl_3$, and extracted with aqueous $NaHCO_3$. The $CHCl_3$ extract was chromatographed on a dry column of silica gel, and the product was eluted with $CHCl_3$ to yield 0.35 g (47%) of **11**: mp 150–151 °C ($n$-$C_4H_9Cl$); IR ($CHCl_3$) 1410, 1265, 1103 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.44 (1 $H_5$, m), 7.85 (1 $H_4$, bd, $J$ = 8 Hz), and 8.47 (1 $H_6$, bd $J$ = 6 Hz); MS $m/e$ 292.8643 ($C_6H_3Cl_4NO_2S$), 175.9574 (M − $CCl_3$), 159.9627 (M − $OCCl_3$), and 116.9068 ($CCl_3$).

**2-Bromo-3-(trifluoromethyl)pyridine (9b).** A solution of $Ac_2O$ (52 mL), 1,1,3,3,tetramethoxypropane (26.4 g, 0.16 mL), **15** (14.5 g, 0.1 mol), and $ZnCl_2$ (1 g) was heated at reflux. After 18 h, the mixture was distilled up to 110 °C at atmospheric pressure. The residue was then cooled to 25 °C and filtered. The clear solution was distilled to yield 3.5 g of **16** (bp 65–93 °C (18 mm)) and 5.3 g of **17** (bp 83–105 °C (0.5 mm)). This material was combined and used in the next step without further purification.

A solution of 30% HBr·AcOH (70 mL) was added dropwise with stirring at 40 °C to a solution of **16** and **17** (8.8 g) in AcOH (40 mL). After the addition, the solution was heated at 55 °C for 2 h, poured onto ice, and neutralized with solid $Na_2CO_3$. The solution was extracted with $CH_2Cl_2$ (3×), and the $CH_2Cl_2$ extracts were dried, filtered, and concentrated to dryness. The residual oil was distilled at 68–71 °C (0.3 mm) to yield 4.2 g (16%) of **9b**: $^1H$ NMR ($CDCl_3$) $\delta$ 7.35 (1 H, dd, $J$ = 4 and 8 Hz), 8.05 (1 H, dd, $J$ = 2 and 8 Hz), 8.45 (1 H, dd, $J$ = 2 and 4 Hz); $^{19}F$ NMR ($CDCl_3$) +40.7 (s).

The exact mass was 256.9130 (calcd for $C_6H_3NBr^{79}SF_3$, 256.9122) and 258.9106 (calcd for $C_6H_3NBr^{81}SF_3$, 258.9102).

**Acknowledgments.** The authors are grateful to Drs. Ralph Hirschmann and E. L. Engelhardt for their interest and encouragement throughout this work. Technical assistance was provided by Mr. K. B. Streeter and Ms. J. Stranick for analytical determinations, Ms. J. S. Murphy for $^{19}F$ NMR spectra, and Mr. R. E. Rhodes for mass spectra.

**Registry No.** **2**, 6298-19-7; **3**, 70682-07-4; **4**, 65753-48-2; **5**, 70682-08-5; **6**, 70682-09-6; **7**, 2769-31-5; **8**, 70682-10-9; **9b**, 70682-11-0; **10**, 70682-12-1; **11**, 70682-13-2; **15**, 34033-79-9; **16**, 70682-14-3; **17**, 70682-15-4; 1,1,3,3-tetramethoxypropane, 102-52-3.

## Phosphoric Acid Systems.[1] 9. Trimethyl Phosphate (TMP) Mediated Halogenative Cleavage of Cyclic Acetals

Sidhaghatta D. Venkataramu, James H. Cleveland, and Donald E. Pearson*

*Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235*

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Both mechanistic and stereochemical aspects involved in the conversion of cyclic acetals **1** to haloesters **2** with various halogenating agents have been intensively examined issues in recent years.[2-8] Traditionally, this synthetically useful transformation[3,5,8,9] has been effected with *N*-bromosuccinimide.[2-5,7,10-14] Reaction conditions

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(13) The conversion of **1** → **2** with NBS has been reported (a) in the presence of a radical initiation (ref 2-4, 7, 10, and 11), (b) by irradiation with UV light (ref 11 and 12), (c) in the presence of an acid acceptor (ref 3 and 4), (d) with a trace of acid (ref 5), and (e) in the presence of $Cu^+$ ions and a radical source (ref 7).

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