from ethanol, mp 77–78°; ir 1760 cm^{-1}; NMR δ 1.10 (s, 9 H) and 1.60 (m, 10 H).

Anal. Calcd for $C_{13}H_{19}BrO_2$: C, 54.36; H, 6.68; Br, 27.82. Found: C, 54.33; H, 6.82; Br, 27.45.

General Procedure for Methanolysis of 2-Oxetanones. The 2-oxetanones could not be easily separated from the diones but were observable by ir bands at 1887, 1828, and 1712 $cm.^{-1}$ Methanolysis of the mixture of dione and 2-oxetanone was accomplished by refluxing this mixture with methanol for 1.5 hr. The β-keto ester revealed bands in the ir at 1748 and 1718 $cm.^{-1}$ Methanolysis of the 1,3-cyclobutanediones required a much longer (1–3 days) reflux period.

Methyl 4-Chloro-3-keto-2,2,5,5-tetramethylhexanoate (XI): bp 90–92° (0.1 mm); NMR δ 1.12 (s, 9 H), 1.40 (s, 3 H), 1.52 (s, 3 H), 3.74 (s, 3 H), and 4.42 (s, 1 H).

Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10; Cl, 15.14. Found: C, 56.53; H, 8.40; Cl, 15.20.

Methyl 4-Chloro-3-keto-2,2,5-trimethylhexanoate (XIII): bp 57–59° (0.5 mm); NMR δ 1.00 (2 d, 6 H), 1.44 (s, 3 H), 1.52 (s, 3 H), 2.40 (m, 1 H), 3.83 (s, 3 H), and 4.40 (d, 1 H).

Anal. Calcd for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.71; Cl, 16.09. Found: C, 54.65; H, 7.80; Cl, 15.52.

Methyl 4-Chloro-2,2-diethyl-3-ketohexanoate (XIII): bp 52–54° (0.05 mm); NMR δ 0.90 (m, 9 H), 2.00 (m, 6 H), 3.76 (s, 3 H), 4.40 (t, 1 H).

Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10; Cl, 15.14. Found: C, 56.64; H, 8.21; Cl, 14.72.

Attempted Isomerization of a 1,3-Cyclobutanedione and a 2-Oxetanone. A 1.0-g portion of a mixture of VIII and the 2-oxetanone obtained from the preparation of VIII was refluxed in hexane for 24 hr. No change in the isomer distribution was observed. The addition of triethylamine and triethylammonium chloride and continued reflux for another 24 hr also caused no change in the isomer distribution.

Acknowledgments. The authors wish to express appreciation to the Robert A. Welch Foundation and the North Texas State University Faculty Research Fund for support of this investigation.

Registry No.—I, 56513-91-8; II, 56513-92-9; III, 56513-93-0; IV, 54363-24-5; V, 54363-23-4; VI, 54363-25-6; VII, 56513-94-1; VIII, 56513-95-2; IX, 56513-96-3; X, 56513-97-4; XI, 56513-98-5; XII, 56513-99-6; XIII, 56514-00-2; dimethyl ketene, 598-26-5; 2-chloro-3,3-dimethylbutanoyl chloride, 52920-18-0; 2-chlorobutanoyl chloride, 7623-11-2; 2-chloropropanoyl chloride, 7623-09-8; 2-bromo-3,3-dimethylbutanoyl chloride, 29336-30-9; isobutyryl chloride, 79-30-1; α-ethylbutyryl chloride, 2736-40-5; cyclohexanecarboxyl chloride, 2719-27-9; 1,2-dichloropropenyl 2-chloropropanoate, 52920-13-5; 1,2-dichlorobutenyl 2-chlorobutanoate, 23649-91-4; 4-chloro-3,3-dimethyl-4-*tert*-butyl-2-oxetanone, 56514-01-3; 4-chloro-3,3-dimethyl-4-isopropyl-2-oxetanone, 56514-02-4; 4-chloro-3,3,4-triethyl-2-oxetanone, 56514-03-5.

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An Efficient α-Halogenation of Acyl Chlorides by *N*-Bromosuccinimide, *N*-Chlorosuccinimide, and Molecular Iodine[1]

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Received April 15, 1975

An efficient procedure (yields ~75%) for the α-halogenation of acyl halides has been demonstrated using *N*-bromosuccinimide, *N*-chlorosuccinimide, and molecular iodine. Thionyl chloride was found to be the most effective solvent for all halogenation reactions and necessary for α-iodination. Various anomalies and possible mechanisms are discussed.

The halogenation of carboxylic acids can be carried out either by free-radical[2] or acid-catalyzed reactions.[3] The former occurs with random orientation and the latter, via the Hell–Volhard–Zelinsky (HVZ) procedure,[3] gives exclusively α-halogenated products only in the case of bromination, but variable selectivity in chlorination, and no reaction at all in iodination.[4]

In an effort to develop new and efficient methods for preparing α-halo acid chlorides, from which a wide variety of compounds may be obtained by replacing both the halogen on the α carbon and on the acyl function, a study was undertaken of the ability of *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), and molecular iodine as α-halogenating agents.

Results and Discussion

α-Bromo acids can be prepared by a multistep procedure, involving alkylation, bromination, deacylation, and hydrolysis.[5] In the more direct method (HVZ),[3] carboxylic acids are treated with free bromine in the presence of a catalyst which can be phosphorus trichloride or phosphorus itself. However, the experimental conditions are sometimes strenuous, often involving high temperature and extended reaction times.

Although NBS is well known as a brominating agent,[6a] there appears to be no report of this reagent being employed to directly brominate acyl chlorides.

We have found that NBS α-brominates a variety of acyl chlorides (formed in situ by the reaction of thionyl chloride[6b] with carboxylic acids, Table I) in good yield.[7] NBS is not only easy to handle but also α-brominates more rapidly and efficiently than molecular bromine, as shown by a comparative study. After 2 hr at 54°, the reaction of *n*-hexanoyl chloride (1) with NBS was almost complete, whereas that with free bromine had only occurred to an extent of ca. 60% (Figure 1). Furthermore, bromination reactions with Br_2 often do not proceed past ca. 80% completion. At 85°, the reaction with NBS was complete after 1.5 hr.[8]

Table I[a]

Compd	Reaction time, hr	Temp,[b] °C	Product	Bp (mm) or mp, °C	Yield, %[c]
1 $CH_3(CH_2)_4COCl$	1.25	85	1a $CH_3(CH_2)_3CH(Cl)COCl$[d]	174–176 (760)[e]	87
	1.50	85	1b $CH_3(CH_2)_3CH(Br)COCl$[f]	45–47 (1.5)	80
	1.50	130	1c $CH_3(CH_2)_3CH(I)COCl$	62–64 (0.5)	80
2 $C_6H_5CH_2CH_2COCl$	2.00	95	2a $C_6H_5CH_2CH(Cl)COCl$[g]	70–71 (0.2)	84
	3.0	85	2b $C_6H_5CH_2CH(Br)COCl$[h]	88–89 (0.35)	71
	3.0	130	2c $C_6H_5CH_2CH(I)COCl$[i]	83–84 (0.5)	75
4 $C_6H_5CH_2COCl$	3.0	85	4a $C_6H_5CH(Br)COCl$	100–102 (5)[j]	75
5 $CH_3(CH_2)_2COCl$	1.50	85	5a $CH_3CH_2CH(Br)COCl$	57–59 (26)[k]	75
	1.50	130	5b $CH_3CH_2CH(I)COCl$[l]	23 (0.1)	69
6 c-$C_6H_{11}COCl$	4.5	85	6a $C_6H_{10}(Br)COCl$	82–85 (5)[m]	58 (70)[n]
7 $CH_3(CH_2)_2CHCOCl$ | CH_3	2.50	85	7a $CH_3(CH_2)_2CCH_3(Cl)COCl$	47–48 (1.0)	79
	0.75	130	7b $CH_3(CH_2)_2CCH_3(I)COCl$	45–46 (0.35)	80[o]
8 $(CH_3)_2CHCOCl$	2.50	85	8a $(CH_3)_2C(Cl)COCl$[p]	58–59 (80)[q]	70
	0.75	130	8b $(CH_3)_2C(I)COCl$[r]	59–60 (0.17)	80[o]
9 $ClCH_2CH_2COCl$	4.0	85	9a $ClCH_2CH(Cl)COCl$[s]	52–54 (16)[t]	70
	2.0	85	9b $ClCH_2CH(Br)COCl$	45 (9)	70
10 $CH_2(CH_2COCl)_2$	1.0	85	10a $CH_2[CH(Br)COCl]_2$		75
11 $(CH_2CH_2COCl)_2$	1.0	85	11a $[CH_2CH(Br)COCl]_2$		60
12 $(C_6H_5)_2CHCOCl$	1.25	85	12a $(C_6H_5)_2C(Cl)COCl$	52–53[u]	82

[a] Typical procedures for each type of halogenation are given in the Experimental Section. Ratio of substrate vs. halogenating agent and solvent was the same in a given type; only the temperature might be changed. [b] Temperatures were that of the heating bath; actual temperatures of the reaction mixture were much lower; for example, they were 85 and 70° for bath temperatures of 130 and 85°, respectively. [c] Yields were based on distilled or recrystallized products; the reactions were complete as per NMR measurement, unless stated otherwise. [d] Amide, mp 56–57° (lit.[13] 57.8–58.2°); anilide, mp 195–197°. [e] Lit.[14] bp 174–176°. [f] Free acid, bp 64–66° (0.075 mm) [lit.[15] 132–140° (15 mm)]. [g] Free acid, mp 48–49°. [h] Amide, mp 125–126° (lit.[16] 126.5–128.5°); methyl ester, bp 92–95° (0.05 mm) [lit.[17] 147–148° (14 mm)]; benzyl ester, bp 143–145° (0.025 mm). [i] Free acid, mp 74.5–75°. [j] Lit.[18] 117° (20 mm). [k] Lit.[19a] 150–152° (760 mm). [l] Free acid, mp 39–39.5° (lit.[20a] 41–42°). [m] Lit.[21] 129–131° (29 mm). [n] Isolated as amide. [o] The reaction was stopped when α-chloro product started to appear; yield was based on the amount of consumed starting material. [p] Free acid, mp 30–31° (lit.[19b] 31°). [q] Lit.[22] 126–127° (113–114 mm). [r] Anilide, mp 126–126.5°. [s] Amide, mp 106–107° (lit.[22] 103°). [t] Lit.[23] 140–144° (720 mm). [u] Lit.[19c] 50–51°.

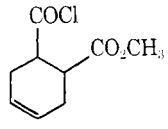
$$CH_3(CH_2)_3CH_2COCl + NBS \xrightarrow{H^+} CH_3(CH_2)_3CHBrCOCl$$
1 1b

Another advantage of the present method is that NBS specifically α-brominates acyl halides and is not reactive toward benzylic-type protons. Thus, 3-phenylpropanoyl chloride (2) reacts with NBS to give 2-bromo-3-phenylpropanoyl chloride (2b), and none of the 3-bromo derivative.[9]

Similarly, the protons of a carboxylic ester are not replaceable by this reaction. When ethyl acetate was treated with NBS, no reaction had occurred after 20 hr at 80°. In the case of the acid chloride of methyl succinate, NBS selectively brominated the carbon atom α to the acyl group.

$$CH_3OOCCH_2CH_2COCl + NBS \xrightarrow{H^+} CH_3OOCCH_2CHCOCl$$
(Br)

Finally, the NMR spectrum of the reaction mixture of the polyfunctional derivative 3 indicated that the acyl chloride



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function was α-brominated first and the carbon–carbon double bond was brominated much later.

The results obtained with NBS led us to extend the method to the α-chlorination of acyl chlorides using *N*-chlorosuccinimide (NCS). Under the same conditions as for NBS, NCS reacted less rapidly.[10] Fortunately, the reaction time was decreased by using a larger amount of NCS and enough thionyl chloride to dissolve NCS completely[11] (Table I).

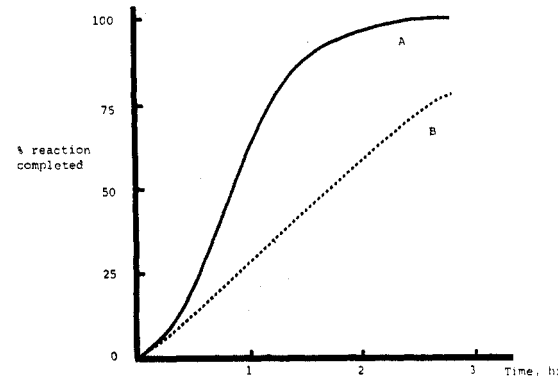


Figure 1. Comparative bromination of *n*-hexanoyl chloride (1) at 54°C: (A) by NBS; (B) by Br_2.

NCS proved to be a very useful chlorinating agent, since it not only gave good yields (70–87%) with various substrates, but was also selective for protons α to the acyl chloride group (for example, 2 gave exclusively 2a). Therefore NCS is superior to the previously employed reactions involving molecular chlorine, which lead not only to α-chloro acids but in some instances to chlorination in various other positions to an appreciable extent.[2d,6b,12]

The fact that benzylic protons, which normally are very susceptible to radical halogenation, are not replaced in the present methods (NBS and NCS) favors an ionic mechanism. The addition of a trace of mineral acid has a strong accelerative effect on the bromination of phenylacetyl chloride (4), while the addition of benzoyl peroxide, a free-radical initiator, considerably suppressed the rate[7a] (Figure 2).

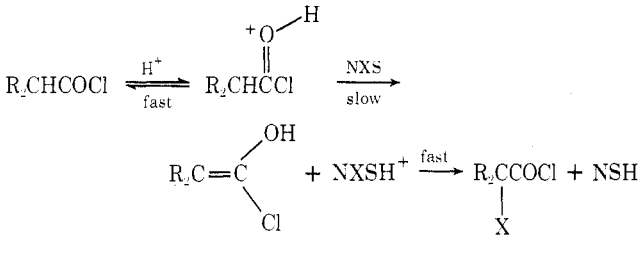
The function of the acid is presumably to enhance the formation of a complex (vide supra).[10] The complex may then undergo halogenation.

The structure of the acyl chloride also has a marked influence on the rate of the reaction. With straight-chain substrates, the time required for the completion of the reaction is essentially the same. Thus, *n*-butanoyl and *n*-hexanoyl chlorides (**5** and **1**, respectively) were completely α-brominated after 1.5 hr. However, when there is a substituent on the α carbon, the reaction is considerably retarded. Cyclohexyl carbonyl and phenylacetyl chlorides (**6** and **4**) required 4.5 and 3.0 hr, respectively, to complete the bromination. Similarly, both 2-methylpentanoyl and 2-methylpropanoyl chlorides (**7** and **8**) were completely chlorinated in 2.5 hr, whereas their straight-chain isomers **1** and **5** needed only 1.25 and 1.50 hr, respectively. It is interesting to note that both functions of a diacyl chloride are α-brominated rapidly. For example, pentyl- and hexyldicarbonyl chlorides (**10** and **11**) required only 1 hr. This might be explained by stabilization of the intermediate complex (vide infra)[10] by internal hydrogen bonding.

It has been assumed and established in some cases that the HVZ method, similar to the acid-catalyzed halogenation of ketones,[24] involves a slow enolization of the acyl chloride (formed in situ), followed by a rapid attack of the halogens on the enol.[25] This entails an independence of the reaction rate on the concentration of halogen.

In the present system it might appear that enolization is not involved in the rate-determining step in that the rate of the reaction depends on the nature of the halogenating agent (NBS reacts faster than NCS) as well as on its concentration (for example, the extent of α-chlorination of diphenylacetyl chloride by 2 equiv of NCS was 80% after 1 hr heating in a 105° bath; when the concentration of NCS was halved, there was only 60% reaction after 1.3 hr.) In addition, an α-alkyl substituted substrate would be expected to more rapidly form an enol and undergo halogenation faster than its straight-chain isomer would; however, the opposite was found to be true.

There are a number of possible rationalizations for these apparent anomalies. The mechanism could involve the *N*-halosuccinimide acting as a base to remove the α hydrogen to form the enol intermediate in the slow step.[10] The enol



would then be halogenated in a rapid step. This proposal would be in accord with the rate dependence on the presence of acid, the nature of the halogenating agent (the highly electron-withdrawing chlorine of NCS would retard the ability of NCS to compete as a base relative to NBS). Further, increasing the substitution around the α position could serve to retard the reaction by hindering the approach of the bulky *N*-halosuccinimide. That NBS is more reactive than either Br_2 or NCS is understandable; the bromine atom of NBS is more positive, therefore more electrophilic, than either Br in molecular bromine or Cl in NCS, based on the relative polarizabilities of the bonds involved.

Another possibility has definition from a proposal made some years ago by Kwart and Scalzi.[10] On the basis of a steric and deuterium isotope study, these authors proposed that the intermediate in the halogenation of acid chlorides

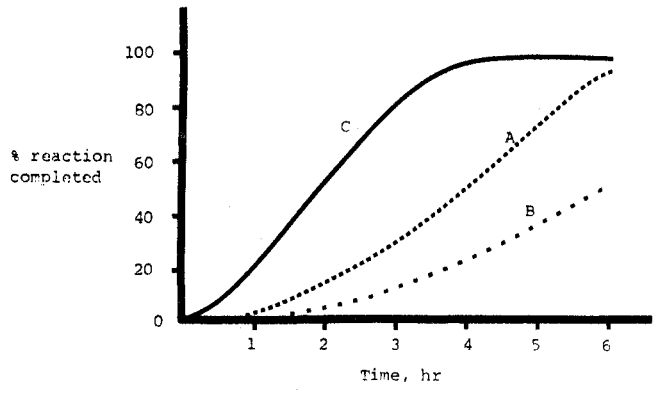
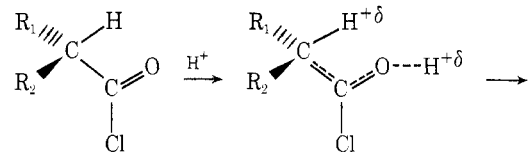


Figure 2. Bromination of phenylacetyl chloride (**4**), 75°: (A) refluxing carbon tetrachloride (1 *M*); (B) as A, benzoyl peroxide added; (C) as A, 1 drop of HBr–HOAc added.

is a cationic complex **13** in which the C_α–H bond of the conjugate acid is highly ionized, yet the proton is still associated with the now-rehybridized α carbon (see **14**). In this



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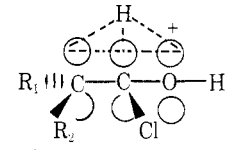

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proposal the rate-determining step would be that of an unusual electrophilic displacement of a proton on the complex **14** by NXS, according to a bimolecular mechanism. This mechanism might explain the steric effect of the α substituent as well as the dependence of the reaction rate on the nature and the concentration of the halogenating agent. Only further study will permit a distinction of these possibilities.

No direct iodination of acyl halides has been reported in literature up to the present time.[26a,b] The classical HVZ method is not applicable to iodine and α-iodo acids are prepared by metathesis from α-bromo acids, the bromide being displaced by iodide ion in aqueous or acetone solution.[26c] However, when a higher bath temperature (130°) is applied and when thionyl chloride is used as solvent (instead of the usual CCl_4) direct iodination results. Attempts to perform the reaction in other polar solvents (e.g., acetonitrile) were not successful even after heating periods up to 5 days. Thionyl chloride presents a special advantage in the iodination procedure reacting instantaneously with hydrogen iodide to give iodine and sulfur.[27] Therefore, in the course of these iodinations there is no net evolution of hydrogen iodide.

Substrates without an α-methyl or phenyl substituent undergo α-iodination smoothly and in good yield (Table I). The reaction was once again selective for protons α to the acyl chloride group (e.g., **2** gave only **2c**). α-Iodacyl chlorides, in parallel with their bromo and chloro counterparts, are easily transformed into a variety of derivatives under very mild conditions.

When the substrate possesses an α-methyl or a second α-phenyl group, iodination is followed by another interesting transformation. For example, the iodination of 2-

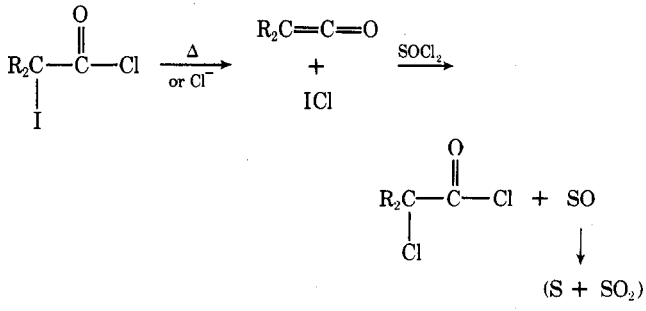
methylpropanoyl chloride (8) gave rise to the following observations (NMR). The spectrum of 8 presents a heptet (δ_{SOCl_2} 2.97, J = 8 Hz, 1 H) and a doublet (δ 1.21, J = 8 Hz, 6 H). When 8 was treated under the usual conditions, a singlet appeared at δ 2.17, which was later shown to correspond to 2-iodo-2-methylpropanoyl chloride (**8b**) (43% after 45-min reaction). Subsequently, the amount of **8b** decreased while another singlet at δ 1.86, shown to be that of 2-chloro-2-methylpropanoyl chloride (**8a**), appeared and grew at the expense of **8b** (35% of **8b** and 19% of **8a** were present in the reaction mixture after 1.5 hr). Finally, 8 and **8b** disappeared completely (10 hr) to leave **8a** as the major product.[28]

The same transformation from the α-iodo to the α-chloro derivatives was observed with 2-methylpentanoyl chloride (7) and diphenylacetyl chloride (**12**). In the latter case, the transformation was so rapid that the α-iodo derivatives could not be isolated, even when the reaction was slowed down by being carried out at lower temperature (70°). An intermediate involving iodine was necessary, however, since when **12** was heated with thionyl chloride in a 110° bath for 1 hr, no reaction occurred.[29]

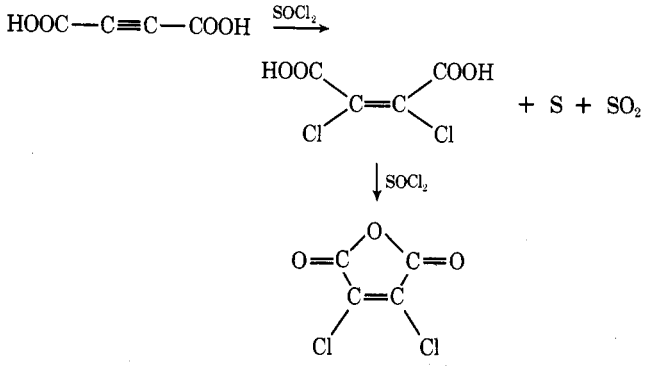
It is clear that the starting acyl chlorides are first α-iodinated in the normal way, then the α-iodo compounds are converted into the α-chloro derivatives, possibly by one of the following mechanisms.

Conceivably iodine was displaced by chloride anions present in the reaction mixture as hydrogen chloride (from the reaction of the starting acid and thionyl chloride). Chloride anion is known to react more rapidly than I^- in aprotic solvents.[30] However, this possibility is not likely, since the reaction would most probably follow an SN2-type displacement rather than an SN1 mechanism (the carbonyl group would destabilize a carbonium ion formed at the α carbon), hence a reaction would be virtually precluded by α-branching. Experimentally, the opposite was found. Moreover, when pure **8b** was dissolved in carbon tetrachloride (without added $SOCl_2$), and the reaction mixture was refluxed with gaseous HCl bubbled through it for 94 hr, no detectable amount of 2-chloro derivative was formed.[31] However, when 2 equiv of thionyl chloride was added to the reaction mixture, a fair amount of **8a** appeared after 3.5 hr at 80°; the transformation was about 40% complete after 26 hr. The reaction was faster when a larger amount of $SOCl_2$ was used. Thus thionyl chloride must actively participate in the reaction.

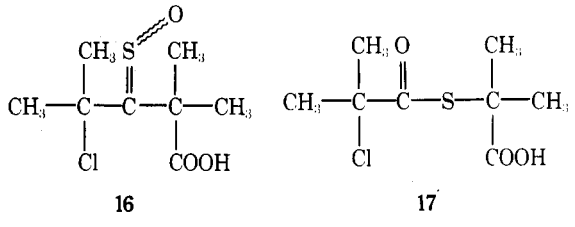
A mechanism which can account for the above facts involves the formation of a ketene, favored by α-branching. The ketene thus formed reacts with thionyl chloride to afford 2-chloroacyl chloride with elimination of SO, the latter being unstable and disproportionating to sulfur[27b] and SO_2.



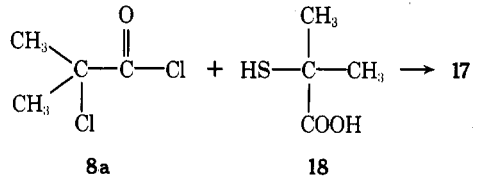
Indeed, when pure diphenylketene (generated by the dehalogenation of 2-bromo-2,2-diphenylacetyl chloride with triphenylphosphine[32] and distilled in vacuo) was treated with $SOCl_2$, there was an exothermic reaction and the final product was identified as the 2-chloro compound **12a**. A similar addition of thionyl chloride to a multiple bond has been reported in the literature.[33] Acetylenedicarboxylic acid reacts with thionyl chloride in dimethylformamide to give dichloromaleic anhydride, a product of cis chlorination.



A minor product was isolated in 3% yield from the iodination of 8. Spectral data were consistent with either of the isomeric structures, sulfine **16**, or thiol ester **17** (see Experimental Section). When **8a** was treated with 2-methyl-2-mercaptopropanoic acid (**18**), a crystalline product was isolated in 95% yield and was found to be identical in all respects (mixture melting point, NMR, ir) with **17**. Attempts

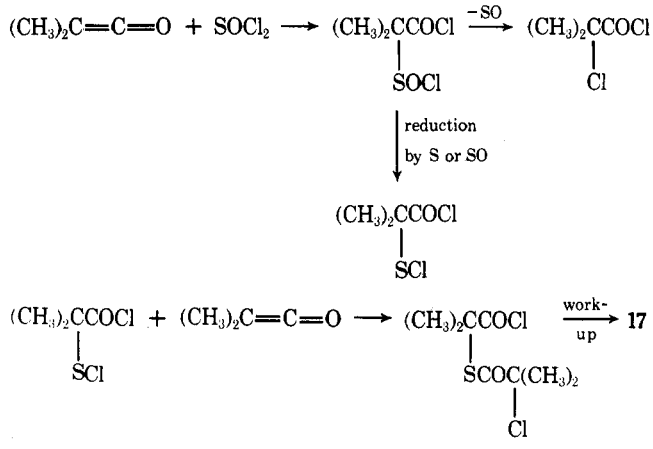


16 17



8a 18

to generate the acyl chloride of 18 from 8 and elemental sulfur in CCl_4, however, were not successful. It is possible that **17**, is formed via a ketene according to the following scheme.[34]



When **1a** and **1b** were treated with NCS or NBS, respectively, for a prolonged period (up to 34 hr), there was no significant change. This further illustrates the specificity of the α-monohalogenation reaction. Iodo derivatives are somewhat more reactive. When **5** was treated with 2 equiv of iodine in thionyl chloride, **5b** was formed first and re-

mained unreactive for ca. 6 hr. Finally, it appeared to undergo diiodination, then dehydroiodination, to a mixture whose NMR was consistent with a mixture of *E* and *Z* vinyl iodides.

In summary, acyl halides can be directly α-halogenated with efficiency and selectivity by means of NBS, NCS, and molecular iodine. In the case of α-methyl- or α-phenyl-substituted substrates, an interesting transformation of the iodo to the chloro compounds occurs.

Experimental Section

Melting points were taken on a Gallenkamp apparatus and are uncorrected. Boiling points are uncorrected. Infrared measurements were performed on a Perkin-Elmer 257 grating spectrophotometer; liquid samples were measured neat on NaCl plates, solid samples as KBr pellets. Mass spectra were recorded at 70 eV on an AEI-MS 902 mass spectrometer. Proton NMR spectra were recorded on a Varian T60 instrument, employing tetramethylsilane as internal standard. Gas chromatographic analyses were carried out on an F & M 5750 research chromatograph, flame ionization detector, SE-30 column. Elemental analyses were performed by MicroAnalyses, Montreal. (Abbreviations: m, medium; s, strong; vw, very weak; w, weak).

2-Chlorohexanoyl Chloride (1a). Hexanoic acid (11.6 g, 0.1 mol) and thionyl chloride (28.8 ml, 0.4 mol) were placed in a 250-ml flask equipped with a magnetic stirring bar, and a condenser with a drying tube. The reaction mixture was stirred and heated in a 70° oil bath. After 0.5 hr, an aliquot of the reaction mixture was submitted to NMR measurement, which showed the disappearance of the triplet at δ 2.40 (-CH_2COOH) and the emergence of a new triplet at δ 2.87 (-CH_2COCl). The flask was removed from the oil bath and cooled to room temperature. To the reaction mixture were added successively finely powdered NCS (26.7 g, 0.2 mol), $SOCl_2$ (20 ml), and concentrated HCl (7 drops). The flask was then returned to the oil bath, the temperature of which was raised to 85°. The actual temperature of the reaction mixture was 70°. After 1.25 hr, the reaction was over, as indicated by the disappearance of the triplet at δ 2.87 and the emergence of a system of two doublets at δ 4.77–4.55 (-CHClCOCl). The solvent was removed under reduced pressure and the solid (succinimide) was collected and washed with CCl_4. The filtrate was fractionally distilled to give 14.7 g (87%) of **1a:** bp 174–176° (760 mm); n_D 1.4458; ir (neat) 1787 vs, 1721 cm^{-1} (shoulder); NMR (neat) δ 4.51 (2 d, *J* = 5.5 and 6 Hz, 1 H, -CHClCOCl); MS *m/e* 170, 168 w (P^+), 135, 133 w ($P - Cl)^+$, 41 base peak $(HC{\equiv}C{=}O)^+$. Anal. Calcd for $C_6H_{10}ClO$: C, 42.62; H, 5.97; Cl, 41.93. Found: C, 42.62; H, 6.07; Cl, 42.25.

The amidation of **1a** (0.8 g, 4.7 mmol) was performed by bubbling dry NH_3 into its anhydrous ether solution (10 ml) at 10° with stirring, until there was a basic reaction to pH paper (10 min). Ether was evaporated, and the white precipitate (0.7 g, quantitative) was washed with ice-cold water, then sublimed at 30° (0.05 mm): mp 56–57° (lit.[13] 57.8–58.2°); NMR δ 7.4 (s, 1 H), 6.53 (s, 1 H), 4.11 (2 d, *J* = 6 and 8 Hz, 1 H, -CHClCO-); MS *m/e* 151, 149 w $(P - Cl)^+$, 44 base peak, $(H_2N{=}C{=}O)^+$.

Anilidation was performed on 0.72 g (4.2 mmol) of **1a,** using 0.4 g (4.3 mmol) of aniline, to give 0.66 g (70%) of the product which was sublimed at 90° (1.25 mm), mp 195–197°.

2-Bromohexanoyl Chloride (1b). The mixture of hexanoic acid (11.6 g, 0.1 mol), CCl_4 (10 ml), and $SOCl_2$ (28.8 ml, 0.4 mol) was stirred at 65° for 0.5 hr. NBS (21.4 g, 0.12 mol), CCl_4 (50 ml), and 48% HBr (7 drops) were added to the mixture. The flask was heated at 70° for 10 min, then at 85° for 1.5 hr. After work-up and fractional distillation in vacuo, **1b** was obtained as a clear, slightly yellow oil (17.1 g, 80%), bp 44–47° (1.5 mm). The decoloration of the product was achieved by using 1.5 ml of a freshly prepared $Na_2S_2O_3$ solution. After distillation, **1b** was obtained (15.75 g, 92% for the decoloration step): bp 45–47° (1.5 mm); $n^{22}D$ 1.4706; d^{24} 1.4017; ir (neat) 1785 cm^{-1}, vs; NMR (neat) δ 4.54 (t, *J* = 6 Hz, 1 H, -CHBrCOCl); MS *m/e* 179, 177 $(P - Cl)^+$. Anal. Calcd for $C_6H_{10}BrClO$: C, 33.75; H, 4.72; Br, 37.42; Cl, 16.60. Found C, 33.42; H, 4.77; Br, 37.29; Cl, 16.74.

The hydrolysis of **1b** (10.28 g, 48.2 mmol) was achieved by treating its acetone (92 ml) solution with 115 ml of a saturated sodium bicarbonate solution (ca. 115 mmol) at 10°. After acidification by concentrated HCl, extraction by $CHCl_3$, and drying over anhydrous $MgSO_4$, the solvent was removed in vacuo to give a colorless liquid (9.36 g, 99.5% yield, 96% pure by gas chromatography). Fractional distillation gave 7.76 g (83%) of 2-bromohexanoic acid, bp 64–66° (0.075 mm) [lit.[15] 132–140° (15 mm)], which was homogeneous by gas chromatography.

Table II

Measurement	Time, hr	NBS % reaction	Br_2, % reaction
1	0.25	6.7	5.2
2	0.50	23.3	15.2
3	0.75	42.6	20.0
4	1.00	64.4	29.3
5	1.25	78.2	37.0
6	1.50	88.9	46.3
7	1.75	93.7	54.1
8	2.08	97.4	60.7
9	2.42	99.3	70.7
10	2.75	100.0	77.0

Comparative Bromination of Hexanoyl Chloride (1) by NBS vs. Molecular Bromine. Hexanoyl chloride (1) was prepared as described above from hexanoic acid (11.6 g, 0.1 mol), carbon tetrachloride (10 ml), and thionyl chloride (28.8 ml, 0.4 mol). To the mixture was added 1.5 ml of xylene which was practically inert to the experimental conditions and used as internal standard. The mixture was then divided into two equal fractions which were placed in two separate flasks. The latter were cooled in an ice bath. Into one of them were introduced bromine (9.6 g, 0.06 mol), CCl_4 (25 ml), and concentrated HBr (3 drops). In the other flask were placed NBS (10.7 g, 0.06 mol), CCl_4 (25 ml), and HBr (3 drops). Condensers with drying tubes were attached and the flasks were placed in the same oil bath (54°). At known intervals of time, aliquots of the reaction mixtures were removed from the flasks and placed in NMR tubes which were dipped in an ice bath to quench the reactions. NMR spectra were recorded, and from the integration curve, the area of the triplet of the product at ca. δ 4.54 (-CHBrCOCl) was compared to that of the aromatic signal of xylene. The ratio was proportional to the extent of the reactions. This ratio increased with time, and at a certain point remained unchanged; the reactions were then considered complete. The results are recorded in Table II.

2-Iodohexanoyl Chloride (1c). Hexanoic acid (11.61 g, 0.1 mol), resublimed iodine (15.23 g, 0.12 g-atom), and thionyl chloride (40 ml, 0.55 mol) were placed in a round-bottom flask equipped with an efficient condenser and a drying tube. The mixture was magnetically stirred and the heating bath was adjusted to 130°. When the reflux was steady, the actual temperature of the reaction mixture was 85°. The reaction was complete after 1.5 hr, as indicated by NMR measurement which was performed and analyzed in the same way as in the preparation of **1a** and **1b.** Thionyl chloride was evaporated under reduced pressure; excess iodine was filtered and washed with carbon tetrachloride. The filtrate was shaken with concentrated $Na_2S_2O_3$ to remove the remaining iodine. The organic layer was separated and dried over anhydrous $MgSO_4$. After solvent evaporation, the product was distilled to yield 21.0 g (80%) of **1c:** bp 62–64° (0.5 mm); $n^{21}D$ 1.5179; NMR (neat) δ 4.94 (t, *J* = 8 Hz, 1 H, -CHClCOCl); MS *m/e* 260 w (cluster of P^+), 98 s $(P - I - Cl)^+$, 41 s $(HC{\equiv}C{=}O)^+$. Anal. Calcd for $C_6H_{10}ClIO$: C, 27.66; H, 3.87; Cl, 13.61; I, 48.72. Found: C, 27.38; H, 3.68; Cl, 13.77; I, 49.10.

2-Chloro-3-phenylpropanoyl Chloride (2a). The procedure was the same as that described for **1a,** except that the temperature was 95°. Thus 7.51 g (0.05 mol) of 3-phenylpropanoic acid gave, after 2.0-hr reaction followed by work-up, 8.51 g (84%) of **2a,** bp 70–71° (0.2 mm), as a clear slightly yellow oil: n_D 1.5340; ir (neat) 1785 vs, 1720 cm^{-1} (shoulder); NMR (neat) δ 7.2 (s, 5 H), 4.59 (2 d, *J* = 6 and 7 Hz, 1 H, -CHClCOCl), 3.5–2.84 (m, 2 H, $C_6H_5CH_2$-); MS *m/e* 202 vw (cluster P^+), 131 s $(P - HCl - Cl)^+$, 91 base peak $(C_7H_7)^+$, 77 m $(C_6H_5)^+$. Anal. Calcd for $C_9H_8Cl_2O$: C, 52.95; H, 3.70; Cl, 35.15. Found: C, 53.23; H, 3.97; Cl, 34.92.

The hydrolysis of **2a** (1 g, 5 mmol) by 1 ml of H_2O was performed by stirring the mixture at room temperature overnight. The mixture was cooled in a Dry Ice bath and then allowed to warm up to room temperature. White crystals were formed and recrystallized from CCl_4–hexane to give 0.94 g (quantitative) of 2-chloro-3-phenylpropanoic acid: mp 48–49°; NMR (neat) δ 12.0 (s, 1 H), 7.30 (s, 5 H), 4.49 (2 d, *J* = 6.5 and 8 Hz, 1 H), 3.59–2.94 (m, 2 H); MS *m/e* 186, 184 vw (P^+), 149 w $(P - Cl)^+$, 91 base peak

($C_7H_7^+$), 77 m ($C_6H_5^+$). Anal. Calcd for $C_9H_9ClO_2$: C, 58.53; H, 4.92. Found: C, 58.14; H, 4.71.

2-Bromo-3-phenylpropanoyl Chloride (2b). The procedure was the same as that for **1b**. The bromination of 15.0 g (0.1 mol) of 3-phenylpropanoic acid gave 17.5 g (71%) of **2b**: bp 88–89° (0.35 mm); ir (neat) 1775 vs, 1720 cm^{-1} (shoulder); NMR (neat) δ 7.17 (s, 5 H), 4.57 (t, J = 8 Hz, 1 H), 3.54–2.84 (m, 2 H); MS m/e 246 w (cluster P^+), 131 s ($P - HCl - Br)^+$, 91 base peak ($C_7H_7^+$), 77 m ($C_6H_5^+$). Anal. Calcd for C_9H_8BrClO: C, 43.67; H, 3.26; Br, 32.28. Found: C, 43.31; H, 3.42; Br, 32.34.

The esterification of **2b** (1.6 g, 6.3 mmol) in CCl_4 (3 ml) by benzyl alcohol (0.7 g, 6.3 mmol) in CCl_4 (3 ml) at room temperature gave 1.565 g (76%) of the ester: bp 144–145° (0.025 mm); NMR (CCl_4) δ 7.17 (s, 5 H), 7.0 (s, 5 H), 4.94 (s, 2 H), 4.3 (t, J = 8 Hz, 1 H), 3.54–2.84 (m, 2 H). The methyl ester was prepared in the same way: bp 92–95° (0.05 mm); $n^{23}D$ 1.5370 [lit.[17] 147–148° (14 mm), $n^{20}D$ 1.5391]; NMR (neat) δ 7.24 (s, 5 H), 4.5 (t, J = 8 Hz, 1 H), 3.5 (s, 3 H), 3.67–3.10 (m, 2 H).

The amide was obtained by bubbling NH_3 for 15 min into a solution of **2b** (2.54 g, 10 mmol) in dry ether (20 ml). The product was recrystallized from aqueous ethanol to give leaves (2.17 g, 89%): mp 125–126° (lit.[16] 126.5–128.5°); ir (KBr) 3420 m, 3280 m, 3180 m, 1675 vs, 1605 cm^{-1}, s; NMR (Me_2SO-d_6) δ 7.9 (s, 1 H), 7.5 (s, 6 H), 4.77 (t, J = 8 Hz, 1 H), 3.75–3.02 (m, 2 H); MS m/e 227, 229 w (P^+), 148 base peak ($P - Br)^+$, 131 s ($C_6H_5CH_2C{\equiv}C{=}O)^+$, 103 s ($C_6H_5CH{=}CH)^+$, 91 s ($C_7H_7^+$), 77 m ($C_6H_5^+$), 44 m ($H_2NC{\equiv}O)^+$. Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.45; H, 4.37; N, 5.86.

2-Iodo-3-phenylpropanoyl Chloride (2c). 3-Phenylpropanoic acid (7.5 g, 0.05 mol) was iodinated by the procedure described above for **1c**. After a 3-hr reaction followed by work-up, 11.0 g (75%) of **2c** was obtained: bp 83–84° (0.05 mm); NMR (neat) δ 7.24 (s, 5 H), 4.84 (t, J = 8 Hz, 1 H), 3.6–4.57 (m, 2 H).

When the reaction was repeated, using only a stoichiometric amount of thionyl chloride (3.6 ml, 0.05 mol) for 7.5 g (0.05 mol) of 3-phenylpropanoic acid and 6.34 g (0.05 g-atom) of iodine in 20 ml of CCl_4, there was no α-iodination, as indicated by the absence of the triplet at δ 4.84 after a heating period of 24 hr. Some side reaction occurred, giving signals upfield from the benzylic proton. No attempt was made to identify the components.

Hydrolysis of **2c** (1.0 g, 3.4 mmol) was performed by the $NaHCO_3$ method as described for **1b**. When solvent was removed on the rotary evaporator, an oily residue remained which solidified on cooling to Dry Ice temperature. The solid was recrystallized from a CCl_4–hexane mixture (1:1) to give 0.9 g (95%) of 2-iodo-3-phenylpropanoic acid: mp 74.5–75°; NMR (CCl_4) δ 11.91 (s, 1 H), 7.42 (s, 5 H), 4.59 (t, J = 8 Hz, 1 H), 3.74–3.02 (m, 2 H); MS m/e 276 w (P^+), 131 s ($P - H_2O - I)^+$, 103 s ($P - HI - COOH)^+$, 91 base peak ($C_7H_7^+$), 77 s ($C_6H_5^+$). Anal. Calcd for $C_9H_9IO_2$: C, 39.15; H, 3.28; I, 45.96. Found: C, 39.09; H, 3.32; I, 45.72.

2-Bromobutanoyl Chloride (5a). Butanoic acid (9.7 g, 0.11 mol) was brominated by NBS in the usual way. The reaction was complete after 1.5 hr. Distillation under reduced pressure gave 15.2 g (75%) of **5a**: bp 57–59° (26 mm) [lit.[19a] 150–152° (760 mm)]; NMR (neat) δ 4.5 (t, J = 8 Hz, 1 H, –CHBrCOCl).

2-Iodobutanoyl Chloride (5b). The iodination of butanoic acid (4.4 g, 0.05 mol) was complete in 1.5 hr, giving 7.9 g (69%) of **5b**: bp 23° (0.1 mm); NMR (CCl_4) δ 4.59 (t, J = 8 Hz, 1 H).

Hydrolysis was performed on 1.0 g (4.3 mmol) of **5b** to give 0.81 g (90%) of 2-iodobutanoic acid which was sublimed at room temperature (0.05 mm) as colorless needles: mp 39–39.5° (lit.[20a] 41–42°); NMR ($CDCl_3$) δ 12.08 (s, 1 H), 4.30 (t, J = 8 Hz, 1 H); MS m/e 214 vw (P^+), 87 m ($P - I)^+$, 41 base peak ($HC{\equiv}C{=}O)^+$. Anal. Calcd for $C_4H_7IO_2$: C, 22.45; H, 3.30. Found: C, 21.91; H, 3.37.

2-Chloro-2-methylpentanoyl Chloride (7a). This compound was obtained in two ways: by the action of NCS or via prolonged iodination.

A. NCS Method. The procedure described for **1a** was used. 2-Methylpentanoic acid (11.6 g, 0.1 mol) was treated with NCS (26.7 g, 0.2 mol), thionyl chloride (40 ml, 0.55 mol), and HCl (7 drops) for 2.5 hr to give 13.35 g (79%) of **7a**: bp 47–48° (1.0 mm); $n^{29}D$ 1.4420; ir (neat) 1775 cm^{-1} vs; NMR (CCl_4) δ 1.84 (s, 3 H). Anal. Calcd for $C_6H_{10}Cl_2O$: C, 42.63; H, 5.96; Cl, 41.94. Found: C, 42.90; H, 6.35; Cl, 41.90.

B. Via Iodination. The starting acid (5.8 g, 0.05 mol) was submitted to α-iodination in the same way as that for **1c**, but the reaction time was increased to 10 hr. NMR measurement showed that the transformation from **7b**, characterized by the singlet at δ_{SOCl_2} 2.16, to **7a** (δ_{SOCl_2} 1.83, s, 3 H), was practically complete. Thionyl chloride was removed, and iodine was filtered and washed with CCl_4. The filtrate was fractionally distilled to give 6.3 g (75%) of an oil, identical in every way with the compound obtained by the NCS method.

2-Iodo-2-methylpentanoyl Chloride (7b). 2-Methylpentanoic acid (11.6 g, 0.1 mol) was iodinated as above, but the reaction was stopped after 0.75 hr, when **7a** started to appear as indicated by the emergence of the singlet at δ 1.83. The mixture was worked up as usual and fractionally distilled to give 7.6 g of **7** and 8.9 g of **7b** (80% yield, based on the amount of consumed starting material): bp 45–46° (0.35 mm); $n^{29}D$ 1.5175; ir (neat) 1760 cm^{-1} vs; NMR (neat) δ 2.04 (s, 3 H). Anal. Calcd for $C_6H_{10}ClIO$: C, 27.66; H, 3.87; Cl, 13.61; I, 48.73. Found: C, 27.88; H, 4.09; Cl, 13.98; I, 49.23.

2-Chloro-2-methylpropanoyl Chloride (8a). This compound was also obtained by two methods.

A. NCS Method. 2-Methylpropanoic acid (4.4 g, 0.05 mol) gave 4.9 g (70%) of **8a**: bp 58–59° (80 mm) [lit.[31] 126–127° (113–114 mm)]; $n^{25}D$ 1.4328; NMR (neat) δ 2.0 (s); ir (CCl_4) 1772 vs, 1740 cm^{-1} (shoulder). Anal. Calcd for $C_4H_6Cl_2O$: C, 34.07; H, 4.29; Cl, 50.29. Found: C, 33.62; H, 4.27, Cl, 49.90.

The corresponding free acid was obtained by hydrolysis, mp 30–31° (lit.[19b] 31°). Anal. Calcd for $C_4H_7ClO_2$: C, 39.20; H, 5.76; Cl, 28.93. Found: C, 38.63; H, 5.34; Cl, 29.28.

B. Via Iodination. The procedure has been described for **7a**. Thus 4.4 g (0.05 mol) of 2-methylpropanoic acid gave 4.7 g (67%) of **8a**, which was identified by spectral data and by its anilide, which sublimed at room temperature (0.025 mm): mp 67–68° (lit.[29b] 67–68°, 69–70°); NMR (CCl_4) δ 9.07 (s, 1 H), 8.24–7.57 (m, 5 H), 8.0 (s, 6 H); MS m/e 199, 197 vw (P^+), 120 base peak ($C_6H_5NHC{\equiv}O)^+$, 77 s ($C_6H_5^+$). Anal Calcd for $C_{10}H_{12}ClNO{\cdot}\frac{1}{2}H_2O$: C, 58.11; H, 6.34; N, 6.78. Found: C, 58.42; H, 5.97; N. 6.82.

During the distillation of **8a**, a white solid was obtained (**17**) at 74° (0.2 mm) in 3% yield: mp 133–134°; ir (KBr) 1700 s, 1670 cm^{-1} s; NMR (CCl_4) δ 10.88 (s, 1 H), 1.74 (s, 6 H), 1.04 (s, 6 H); MS m/e 226, 224 w, 198, 196 w, 147 m, 87 s, 77 base peak, 41 s. Exact mass measurement: calcd 224.0273, found 224.0290. Anal. Calcd for $C_8H_{13}OClS$: C, 42.76; H, 5.83; Cl, 15.78; S, 14.27. Found: C, 42.70; H, 5.41; Cl, 15.54; S, 14.42.

Preparation of Thiol Ester 17. In a 100-ml flask equipped with a magnetic stirring bar, a reflux condenser, and a drying tube were placed 2-mercapto-2-methylpropanoic acid (**18**, 1.0 g, 8.3 mmol), 2-chloro-2-methylpropanoyl chloride (**8a**), and CCl_4 (40 ml). The mixture was refluxed in an 80° oil bath overnight. The solvent was removed on the rotary evaporator to give a white solid which was then recrystallized from CCl_4, 1.95 g (95%). This compound was identical with **17** (mixture melting point, ir, NMR).

2-Iodo-2-methylpropanoyl Chloride (8b). The iodination of 2-methylpropanoic acid (4.4 g, 0.05 mol) was stopped when the singlet at δ 1.86 of **8a** started to appear (ca. 0.75 hr). After work-up, fractional distillation gave 4 g (80%) based on the amount of consumed starting material of **8b**: bp 59–60° (0.17 mm); NMR (neat) δ 2.37 (s). Anal. Calcd for C_4H_6ClIO: C, 20.67; H, 2.60; Cl, 15.25; I, 54.59. Found: C, 20.46; H, 2.51; Cl, 15.53; I, 54.19.

The anilidation was performed on a solution of **8b** (0.781 g, 3.36 mmol) in ether (5 ml) by aniline (0.313 g, 3.36 mmol) dissolved in ether (5 ml). When aniline was added dropwise to the starting material, a dark blue color appeared, then turned to dark orange. The precipitate formed was filtered and washed with ether. Ether was removed from the filtrate, and the solid residue was recrystallized from CCl_4 to give long needles (0.84 g, 86%) of anilide: mp 126–126.5°; NMR (acetone-d_6) δ 9.67 (s, 1 H), 8.34–7.57 (m, 5 H), 2.4 (s, 6 H); MS m/e 289 s (P^+), 169 w [$(CH_3)_2CI]^+$, 162 w ($P - I)^+$, 92 w ($C_6H_5NH)^+$, 77 w ($C_6H_5^+$), 70 m [$(CH_3)_2C{=}C{=}O]^+$, 41 s ($CH_3C{=}CH_2)^+$. Anal. Calcd for $C_{10}H_{12}INO$: C, 41.54; H, 4.18; I, 43.89; N, 4.84. Found: C, 41.78; H, 4.19; I, 43.31; N. 5.10.

Attempted Iodination of 8 in Acetonitrile. 2-Methylpropanoic acid (4.4 g, 0.05 mol), thionyl chloride (3.6 ml, 0.05 mol), and CCl_4 (5 ml) were refluxed for 0.5 hr. NMR measurement showed a complete transformation to **8**. To the reaction mixture was added iodine (6.35 g, 0.05 g-atom), acetonitrile (25 ml), and HI (5 drops). The mixture was refluxed in a 85° oil bath. NMR measurement showed that the doublet signal (δ 8.72, J = 6 Hz) of the methyl group of **8** remained almost unchanged, for 114 hr, indicating no α-halogenation.

Attempted Transformation of 8b by HCl in the Absence of $SOCl_2$. Dry HCl was bubbled into a solution of **8b** (1 g, 4.2 mmol) in CCl_4 (10 ml). The solution was heated to 85°. After 94 hr, no detectable amount of **8a** was formed as evidenced by NMR measurement.

Transformation of 8b into 8a by $SOCl_2$ in the Absence of HCl. Dry nitrogen was passed through a solution of **8b** (1 g, 4.2

mmol) in CCl_4 (10 ml) for 5 hr to flush any HCl which might be present. Thionyl chloride (20 ml) was added to the solution which was then heated to 85°. After 26 hr, ca. 40% of **8b** was transformed to **8a**, as per NMR measurement.

2,3-Dichloropropanoyl Chloride (9a). This compound was prepared by the procedure described for **1a**. Thus 3-chloropropanoic acid (5.4 g, 0.05 mol) gave 5.6 g (70%) of **9a**: bp 52–54° (16 mm) [lit.[23] 140–144° (720 mm)]; $n^{20}D$ 1.4764; NMR (neat) δ 4.87 (2 d, J = 5 and 6.5 Hz, 1 H, –CHClCOCl). Its amide was prepared by the usual method: mp 106–107° (lit.[22] 103°); NMR (acetone-d_6) δ 7.04 (broad s, 2 H), 4.54 (t, J = 5 Hz, 1 H); MS m/e 141 (cluster P^+), 108, 106 m $(P - Cl)^+$, 89 w $(P - Cl - OH)^+$, 62 s $(P - Cl - CONH_2)^+$, 44 base peak $(H_2NC{\equiv}O)^+$. Anal. Calcd for $C_3H_5Cl_2O$: C, 25.38; H, 3.55; N, 9.86. Found: C, 25.03; H, 3.61; N, 10.11.

2-Chlorodiphenylacetyl Chloride (12a). This compound was prepared by two different routes.

A. NCS Method. The usual procedure was followed. The proton signal was shifted from δ 5.0 (starting acid) to δ 5.25 (acyl chloride). The latter signal disappeared after a heating period of 1.5 hr at 85°. After work-up, the product was obtained and recrystallized from CCl_4 to give 21.8 g of **12a** (82% yield from 21.2 g, 0.1 mol of diphenylacetic acid): mp 52–53° (lit.[19] 50–51°); NMR ($CDCl_3$) δ 7.4 (s).

B. Via Iodination. The usual procedure of iodination was performed on 5.3 g (0.025 mol) of diphenylacetic acid at 130° (bath temperature). After 1.3 hr, the reaction was complete; the NMR spectrum of the reaction mixture was very clean and showed only one singlet at δ 7.4. Iodine was filtered (2.2 g of iodine was recovered from the starting amount of 3.7 g). After work-up, 7.0 g of a white solid was obtained which was identified as **12a**: mp 52–53°; ir (KBr) 1765 cm^{-1} s; MS m/e 266, 264 (P^+), 201, 203 s $(P - COCl)^+$, 194 s $(C_6H_5)_2C{=}C{=}O)^+$, 166 s $(C_{13}H_{10}^+)$, 165 base peak. Anal. Calcd for $C_{14}H_{10}Cl_2O$: C, 63.42; H, 3.80; Cl, 26.74. Found: C, 63.51; H, 3.62; Cl, 26.85.

The reaction was repeated, but the temperature was lowered to 70°. When about half of the starting material had reacted (ca. 5 hr) the reaction was stopped and worked up, but no iodo derivative could be isolated.

C. Via the Reaction of Ketene and Thionyl Chloride. Diphenylketene was generated from the reaction of 2-bromodiphenylacetyl chloride (30.8 g, 0.1 mol) and triphenylphosphine (30.0 g, 0.11 mol) in dry benzene.[31] The ketene was distilled in vacuo to give 12.6 g (65%) of an orange liquid: bp 73–75° (0.1 mm) [lit.[31] 95–96° (0.5 mm)]; ir (neat) 2095 vs, 2054 cm^{-1} w; NMR (CCl_4) δ 7.17.

Diphenylketene (9.4 g, 0.48 mol) was added rapidly into $SOCl_2$ (15 ml). An exothermic reaction took place and the orange color of ketene faded. The solution was refluxed for 3 hr. Work-up was performed as described above, to give 8.9 g (70%) of a product which was identical with **12a** by spectral data.

Acknowledgment. We thank the National Research Council of Canada for financial support of this work and Dr. James P. Snyder, University of Copenhagen, for valuable discussions.

Registry No.—**1**, 142-61-0; **1a**, 43056-19-5; **1b**, 42768-46-7; **1c**, 54468-31-4; **2a**, 54468-36-9; **2b**, 42762-86-7; **2c**, 54468-37-0; **4a**, 19078-72-9; **5a**, 22118-12-3; **5b**, 54468-34-7; **6a**, 29548-87-6; **7a**, 54468-32-5; **7b**, 54468-33-6; **8a**, 13222-26-9; **8b**, 54468-35-8; **9a**, 7623-13-4; **9b**, 29548-84-3; **10a**, 29548-85-4; **11a**, 29548-86-5; **12a**, 2902-98-9; **17**, 56348-63-1; **18**, 4695-31-2; hexanoic acid, 142-62-1; 2-chlorohexanamide, 56348-64-2; 2-chlorohexananilide, 56348-65-3; *N*-bromosuccinimide, 128-08-5; *N*-chlorosuccinimide, 128-09-6; 2-bromohexanoic acid, 616-05-7; iodine, 7553-56-2; 3-phenylpropionic acid, 501-52-0; 2-chloro-3-phenylpropanoic acid, 20334-70-7; benzyl 2-bromo-3-phenylpropionate, 56348-66-4; methyl 2-bromo-3-phenylpropionate, 3196-22-3; 2-bromo-3-phenylpropionamide, 56348-67-5; 2-iodo-3-phenylpropanoic acid, 54468-38-1; butanoic acid, 107-92-6; 2-iodobutanoic acid, 7435-10-1; 2-methylpropanoic acid, 97-61-0; 3-methylpropanoic acid, 79-31-2; 2-chloro-2-methylpropanoic acid, 594-58-1; 2-chloro-2-methylpropionanilide, 2322-58-9; 2-iodo-2-methylpropionanilide, 54468-39-2; 3-chloropropanoic acid, 107-94-8; diphenylacetic acid, 117-34-0; diphenylketene, 525-06-4.

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(8) NBS was partially decomposed into Br_2 under the experimental conditions used; the observed rate was therefore a combination of the reaction with NBS and the relatively slower one with Br_2.

(9) This was demonstrated as follows. The side chain protons ($-CH_2CH_2-$) of the starting material **2** form an A_2B_2 system (δ 3.23–7.35) which was transformed into an ABX system ($-CH_2CHBr-$) in the product and could be analyzed by first-order splitting: δ (CCl_4) 4.65 (H_X), 3.71 (H_A), and 3.18 (H_B), $J_{AX} = J_{BX} = 7$, $J_{AB} = 14$ Hz. The mass spectrum of the product was characterized by a peak at m/e 91 (base peak, $C_7H_7^+$).[9b] The absence of $C_7H_8Br^+$, which would give a pair of peaks of equal intensity at m/e 169 and 171, was further demonstrated. (b) This ion could be the benzylium or tropilium ion: J. Winkler and F. W. McLafferty, *J. Am. Chem. Soc.*, **95**, 7533 (1973). (c) When the HVZ method was applied to **2**, followed by esterification, a mixture of α- and β-bromo compounds was formed but could not be separated by fractional distillation.[17]

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(27) (a) This reaction presumably proceeds according to the equation

$$2SOCl_2 + 4HI \rightarrow S^0 + SO_2 + 2I_2 + 4HCl$$

(b) The presence of sulfur was shown by its reaction with triphenylphosphine to give triphenylphosphine sulfide.

(28) There is no similar transformation from α-bromo to α-chloro derivatives, e.g., when **8** is brominated by Br_2 or NBS in thionyl chloride.

(29) In order to ascertain whether or not diphenyacetic acid was chlorinated

directly by thionyl chloride, the following experiment was performed. The starting acid (5.3 g, 0.025 mol) was treated with $SOCl_2$ (10 ml) at 110°. After 1.5 hr the NMR spectrum of the reaction mixture showed that the α proton was not replaced. Therefore **12a** could not be obtained in the absence of iodine. At a higher temperature (130°) and upon a longer period of heating (overnight) there was ca. 40% α-chlorination.

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Hydroxylation of Carbonyl Compounds via Silyl Enol Ethers[1a]

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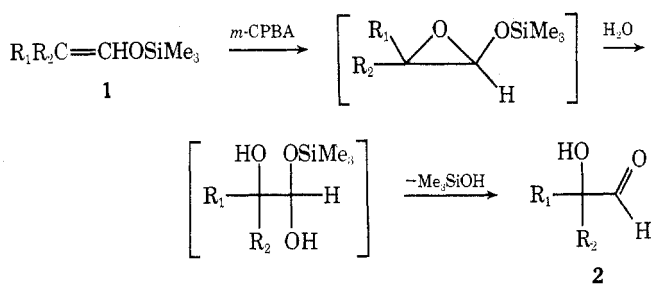
Received September 4, 1974

Silyl enol ethers **1**, which are readily available from the corresponding aldehydes, react rapidly with *m*-chloroperbenzoic acid to afford the protected α-hydroxy aldehydes **3** in good yield. Treatment of **3** with acetic anhydride and triethylamine produces α-acetoxy aldehydes **5**. This sequence provides a simple procedure for α-hydroxylation of aldehydes. Silyl enol ethers of ketones **10** are converted directly to α-siloxy ketones **11** with *m*-chloroperbenzoic acid representing a significant improvement over the usual enol ether or acetate procedure.

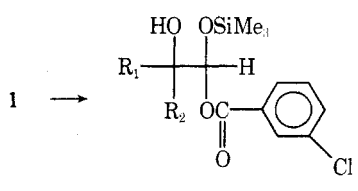
The effectiveness of trimsyl[1d] enol ethers **1** as masked aldehydes, ketones, and even acids or esters in reactions with electrophiles such as halogens or NOCl has recently been demonstrated.[2] We have now examined the reaction of **1** with peracids, as a potential route to siloxy epoxides or to α-hydroxy carbonyl compounds[3] which are of current interest in sugar synthesis and as precursors to β-hydroxy-α-amino acids.[4] Until recently there were no satisfactory methods available for the synthesis of α-hydroxy aldehydes.[5a] Several procedures have now been described, but they represent homologation reactions.[4,5]

A simple operation was envisioned which would proceed via the epoxidation of trimsyl enol ethers **1** with *m*-chloroperbenzoic acid (*m*-CPBA) followed by hydrolysis and β-cleavage of trimsyl alcohol[6] to afford the desired product **2** as shown in Scheme I. However, the observed product was

Scheme I



not the hydroxy aldehyde **2**, but the acetal derivative **3**, which is probably generated by opening of the intermediate epoxide by *m*-chlorobenzoic acid or by trapping of an intermediate cation by this acid. The in situ ring opening of α-

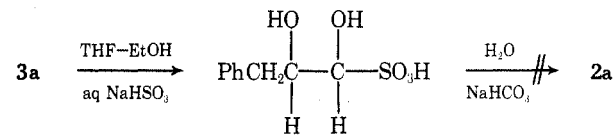


alkoxy epoxides, derived from vinyl ethers, by carboxylic acids is a well-known reaction.[7] Attempts to trap the epoxide as the aldehyde by reaction in aqueous THF and as the dimethyl acetal by reaction in methanol afforded uncharacterized mixtures. Hydrogen peroxide (30%) in THF produced only the parent aldehyde via hydrolysis.

Equimolar amounts of **1** and *m*-chloroperbenzoic acid reacted rapidly at room temperature in dichloromethane. After 1 hr, work-up yielded **3** in high yield (Table I). The structure of the product was confirmed by ir, NMR, and mass spectral data. The technique is applicable to a wide range of aldehydes. Thus, R may be alkyl, aryl, or hydrogen. Particularly noteworthy is the presence of a double bond (entry **1f**) and an ester function (**1c**).

It is well known that α-hydroxy aldehydes **2** are quite unstable and rapidly rearrange to hydroxy ketones, dimerize, and polymerize.[5] Generally, compounds **2** are generated in a protected form such as an acetal and converted to the parent **2** only with difficulty.[5] Similar difficulties were encountered in this work. Thus, when **3a** was treated with fluoride ion in Me_2SO or THF,[7] hydrochloric acid in methanol, or aqueous sodium hydroxide in THF, the desired aldehyde **2a** was not obtained. Pyrolysis of **3a** also failed to produce **2a** by expulsion of trimsyl *m*-chlorobenzoate. Finally, an effort to convert **3a** to the siloxy derivative of **2a** by generation of the alkoxide ion by LiH followed by intramolecular silicon transfer also failed. No effort was made to determine the course of these reactions once it was found that the desired transformation was not occurring.

An uncharacterized red oil was obtained from phenylhydrazine and **3e** rather than the desire osazone.[9a] Treatment of **3a** with a standard solution of sodium bisulfite afforded sulfonate **4**.[9b] However, when **4** was stirred with aqueous



sodium bicarbonate, **2a** was not obtained, but instead an uncharacterized mixture which appeared to contain mostly the dimer of **2a** was recovered. Attempted protection of the hydroxyl function of **3** as an *O*-methyl ether by reaction with methyl Meerwein reagent or methyl iodide and silver oxide or sodium hydride resulted in polymeric products.

Successful deblocking of **3** to generate acetoxy aldehyde