A Facile Method for the Oxidation of Alcohols

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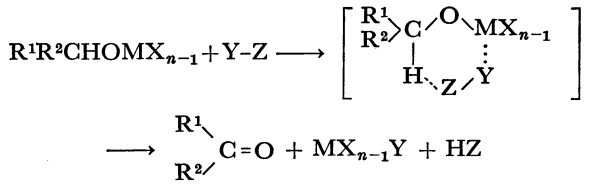
Trialkyltin alkoxides, prepared from alcohols and trialkyltin methoxide by azeotropical removal of methanol, are easily oxidized by bromine in the presence of trialkyltin methoxide, a hydrogen bromide captor, to give the corresponding aldehydes or ketones in good yields. Alcohols are oxidized directly in one step to the corresponding carbonyl compounds by utilizing bis(tributyltin) oxide and bromine.

Selective oxidation of alcohols to the corresponding aldehydes or ketones is important in organic synthesis, and a number of methods have been reported. Reagent such as aluminum triisopropoxide (the Oppenauer oxidation),[1] CrO_3–AcOH complex (Jones reagent),[2] CrO_3–pyridine complex (Collins reagent),[3] dicyclohexylcarbodiimide–dimethylsulfoxide,[4] dimethylsulfide–chlorine or *N*-chlorosuccinimide[5] and others[6] are commonly employed for oxidizing alcohols to aldehydes or ketones, but they bring about certain difficulties. For example, further oxidation of the desired aldehyde to carboxylic acid and of carbon–carbon double bonds or isomerization of carbon–carbon double bonds sometimes takes place reducing the yields of the desired aldehydes or ketones. This prompted us to look for efficient reagents for the oxidation of alcohols to the corresponding aldehydes or ketones.

The study was initiated to examine the effective combination of a metal alkoxide ($R^1R^2CHOMX_{n-1}$) and an oxidant (Y-Z) based on the following consideration: If oxidant Y has a strong affinity to alkoxide M and oxidant Z also has an affinity toward hydride, the oxidation would be effectively promoted *via* 6-membered cyclic intermediate to give the desired carbonyl compound accompanied by the formation of $MX_{n-1}Y$ and HZ as illustrated in the following scheme.

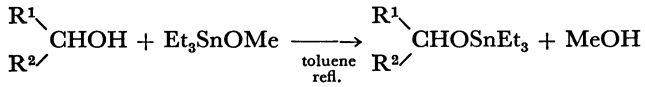


After several trials with cinnamyl alcohol as a model alcohol, cinnamaldehyde was obtained in a moderate yield when triethyltin cinnamyl oxide was treated with bromine[7] as briefly reported in a previous communication.[8] In this report, details of the oxidation are described with additional results.

The starting materials, triethyltin alkoxides, were prepared according to a modification of the method in literature.[9] Alcohol was allowed to react with triethyltin methoxide[10] in toluene under refluxing, the methanol formed being removed continuously. The corresponding triethyltin alkoxide was obtained in a good yield after distillation under reduced pressure (Table 1).

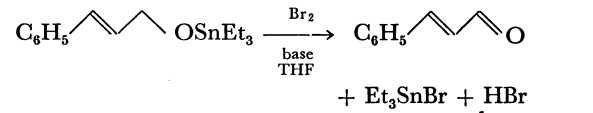
It was found that, in the absence of the hydrogen bromide captor, the starting triethyltin alkoxide was destroyed by the rapid reaction with hydrogen bromide to form triethyltin bromide and the alcohol, and that in order to improve the yield of the carbonyl compound it is necessary to capture hydrogen bromide produced at the same time. Of several hydrogen bromide captors examined, the best result was obtained when

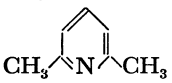
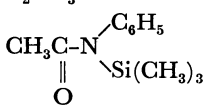
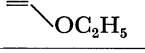
Table 1. Preparation of triethyltin alkoxides



Alcohol	Reaction time (h)	Isolated yield (%)	Bp (mmHg)
Geraniol	8	92	134—6 °C (1.0)
Cinnamyl alcohol	2	84	145—7 °C (0.75)
(*E*)-2-Hexen-1-ol	14	78	105—7 °C (2.4)
Piperonyl alcohol	6	86	153—6 °C (0.8)
Benzyl alcohol	9	78	108 °C (0.7)
1-Phenylethanol	5	78	108—9 °C (1.4)
2-Octanol	4	86	108—9 °C (1.8)

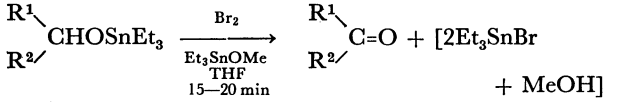
Table 2. Examination of hydrogen bromide captors



Base	Yield (%)[a]	Base	Yield (%)[a]
Et_3SnOMe	82	K_2CO_3	33
	47		trace
NaH	43		trace

a) Yield determined by GLC.[11]

Table 3. Oxidation of triethyltin alkoxides



Alcohol	Yield (%)
Geraniol	94[a]
Cinnamyl alcohol	92[b]
(*E*)-2-Hexen-1-ol	71[b]
Piperonyl alcohol	96[a]
Benzyl alcohol	81[b]
1-Phenylethanol	79[b]
2-Octanol	85[b]

a) Isolated yield. b) Yield determined by GLC.[11]

triethyltin methoxide was employed as a captor (Table 2).

The effect of the solvent on the oxidation of triethyltin 1-phenylethoxide with bromine was studied in tetrahydrofuran (THF), dichloromethane and benzene, and the corresponding ketone, acetophenone, was obtained in 78%, 70% and 66% yields, respectively.

Optimum yield was obtained when a THF solution of bromine was added dropwise to a THF solution of triethyltin alkoxide in the presence of triethyltin methoxide as a hydrogen bromide captor. The oxidation of various triethyltin alkoxides was attempted and the corresponding aldehydes or ketones were obtained in good yields (Table 3).

Similarly, tributyltin alkoxide, easily prepared from bis(tributyltin) oxide and an alcohol, was oxidized with bromine in the presence of tributyltin methoxide as a hydrogen bromide captor. As an example, tributyltin benzyl oxide was oxidized to give benzaldehyde in 82% yield.

$$C_6H_5CH_2OSnBu_3 \xrightarrow[Bu_3SnOMe,\ THF]{Br_2} C_6H_5CHO + [2Bu_3SnBr + MeOH]$$

The yield decreased when chlorine or iodine was employed as an oxidant instead of bromine.

It is remarkable that the reaction is completed as soon as the titration of a bromine solution is over. It is noteworthy that the oxidation of geraniol affords geranial in a high yield, no by-products such as a further oxidized product (geranic acid), an isomerized product (neral) and brominated products formed by the addition of bromine to the olefinic linkages being detected.

The present method involves the following two processes: (1) Preparation of trialkyltin alkoxides from alcohols and trialkyltin methoxide or bis(trialkyltin) oxide, and (2) oxidation of trialkyltin alkoxides to the carbonyl compounds with bromine in the presence of trialkyltin methoxide. In order to find a one step procedure for the oxidation of alcohols, oxidation with bromine utilizing bis(tributyltin) oxide[12] was studied on the basis of the following: Bis(tributyltin) oxide reacts with alcohols to give the corresponding tributyltin alkoxides and tributyltin hydroxide,[13] and with hydrogen halide to give tributyltin halide and tributyltin hydroxide. Thus tributyltin alkoxides would be formed *in situ* from alcohols and bis(tributyltin) oxide, and the alkoxides would be similarly oxidized with bromine in the presence of bis(tributyltin) oxide, a hydrogen bromide captor.

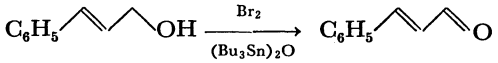
Actually, cinnamaldehyde was obtained in 84% yield by adding a bromine solution into a solution of an equimolar amount of cinnamyl alcohol in the presence of bis(tributyltin) oxide. It was found that THF is also better than benzene or dichloromethane as a solvent similarly to the case of oxidation of isolated trialkyltin alkoxides (Table 4).

In the case of the oxidation of 2-octanol, 2-octanone was obtained only in 60% yield under these conditions. After several trials it was found that the optimum yield is obtained for 2-octanone when the mole ratio of alcohol, bis(tributyltin) oxide and bromine is 1 : 2 : 2. In the case of hindered alcohols such as 1-phenylethanol, benzhydrol and 3β-cholestanol, the yields were improved by treatment of alcohol with bis(tributyltin) oxide in the presence of molecular sieves[14] at 50—60 °C for several hours before the addition of bromine. The oxidation of several alcohols was examined under these conditions and the corresponding aldehydes or ketones were obtained in good yields (Table 5).

By this procedure, alcohols are directly oxidized by bromine in the presence of bis(tributyltin) oxide without isolation of the intermediates, trialkyltin alkoxides, which was necessary in the former procedure.

The present procedures utilizing organotin derivatives and bromine as an oxidant provides convenient and efficient methods for the oxidation of alcohols to the corresponding aldehydes or ketones. It is expected that these methods will find widespread use.

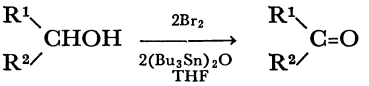
Table 4. Solvent effect in the oxidation of alcohols with bromine using bis(tributyltin) oxide



Solvent	Yield (%)[a]
THF	84
CH_2Cl_2	53
C_6H_6	47

a) Yield determined by GLC.[11]

Table 5. Direct oxidation of alcohols with bromine in the presence of bis(tributyltin) oxide



Alcohol	Yield (%)	
Cinnamyl alcohol	85[b]	
2-Octanol	90[b]	
(*E*)-2-Hexen-1-ol	81[b]	
Benzyl Alcohol	89[b]	
Piperonyl alcohol	83[a]	
1-Phenylethanol	62[b]	(88)[b]
Benzhydrol		(62)[b]
3β-Cholestanol		(89)[a]

a) Isolated yield. b) Yield determined by GLC.[11] Values in parentheses indicate the yields when alcohols were allowed to react with bis(tributyltin) oxide in the presence of molecular sieves before the addition of bromine.

Experimental

Preparation of Triethyltin Alkoxides. A solution of an alcohol (20 mmol) and triethyltin methoxide (24 mmol) in toluene (50 ml) was refluxed for 2—14 h (Table 1) under an argon atmosphere, and methanol formed was azeotropically removed. After removal of the solvent, the corresponding triethyltin alkoxide was obtained by distillation under reduced pressure.

General Procedure for Oxidation of Triethyltin Alkoxides with Bromine. To a THF solution of triethyltin alkoxide (1 M) and triethyltin methoxide (1.2—1.7 M) was added dropwise a THF solution of bromine (1 M) at room tem-

perature under an argon atmosphere. As soon as the addition of bromine was over, the reaction mixture was quenched with a 5% aq. $Na_2S_2O_3$ solution and a 5% aq. NaOH solution, and the resulting mixture was extracted with ether. The ethereal layer was washed with a 5% aq. NaOH solution and brine, and dried over anhydrous Na_2SO_4. The yields of the corresponding carbonyl compounds were determined by vapor phase chromatographic analysis or by isolation using thin layer chromatography (silica gel).

Oxidation of Triethyltin Geraniloate with Bromine. To a solution of triethyltin geraniolate (679 mg, 1.89 mmol) and triethyltin methoxide (754 mg, 3.18 mmol) in THF (20 ml) was added drop by drop a solution of bromine (310 mg, 1.94 mmol) in THF (10 ml) over a period of 15 min at room temperature under an argon atmosphere. The reaction mixture was then quenched with a 5% aq. $Na_2S_2O_3$ solution (5 ml) and a 5% aq. KOH solution (20 ml). The resulting mixture was extracted with ether (60 ml), and the ethereal layer was washed with a 5% aq. KOH solution (20 ml) and with brine (20 ml). After evaporation of the solvent, geranial (269 mg, 94%), identified by NMR spectrum and GLC analysis on comparison with an authentic graphy.

Preparation of Tributyltin Benzyl Oxide. A solution of benzyl alcohol (2.67 g, 25.5 mmol) and bis(tributyltin) oxide (7.61 g, 12.8 mmol) in benzene (70 ml) was refluxed for 4 h under an argon atmosphere; water was continuously removed. After removal of the solvent, tributyltin benzyl oxide was isolated by distillation under reduced pressure (7.61 g, 75%, bp 140—142 °C/0.9 Torr).

Oxidation of Tributyltin Benzyl Oxide with Bromine. To a THF (20 ml) solution of tributyltin benzyl oxide (461 mg, 1.16 mmol) and tributyltin methoxide (374 mg, 1.17 mmol) was added a THF (10 ml) solution of bromine (185 mg, 1.16 mmol) within a period of 20 min at room temperature under an argon atmosphere. After a similar work-up, GLC analysis indicated a yield of 82% of benzaldehyde (pentylbenzene as an internal standard with 10% Carbowax 20 M column).

General Procedure for the Oxidation of Alcohols with Bromine Utilizing Bis(tributyltin) Oxide. A solution of alcohol (1 M) and bis(tributyltin) oxide (2 M) in THF was stirred for 30 min at room temperature or for 1—2 h at 50—60 °C in the presence of molecular sieves (3 A) (in the case of hindered alcohols) under an argon atmosphere. To the mixture was added dropwise a THF solution of bromine (2 M) in the course of 30 min at room temperature. *Work-up (a) Isolation of the Product*: To the reaction mixture was added powdered $Na_2S_2O_3$, and the resulting suspension was stirred for 30 min. After filtration, the solvent was evaporated under reduced pressure. To the remaining residue were added NH_4F, H_2O and ether. The mixture was stirred for 30 min, and the precipitate formed was filtered off. The ethereal layer was washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent, the corresponding carbonyl compound was isolated by preparative thin layer chromatography or column chromatography (silica gel). *(b) Determination of the Product by GLC*: The reaction mixture was quenched with a 5% aq. NaOH solution and a 5% aq. $Na_2S_2O_3$ solution, the resulting mixture being extracted with ether. The ethereal layer was washed with a 5% aq. NaOH solution and brine, and dried over anhydrous Na_2SO_4. The yield was indicated by GLC analysis with an internal standard.

Oxidation of 2-Octanol with Bromine Utilizing Bis(tributyltin) Oxide. A solution of 2-octanol (127 mg, 0.97 mmol) and bis(tributyltin) oxide (1260 mg, 2.17 mmol) in THF (20 ml) was stirred for 30 min at room temperature under an argon atmosphere. To the solution was added dropwise a solution of bromine (347 mg, 2.17 mmol) over a period of 30 min. After quenching with a 5% aq. $Na_2S_2O_3$ solution (5 ml) and a 5% aq. NaOH solution (20 ml), the mixture was extracted with ether, and the ethereal layer was washed with a 5% aq. NaOH solution (20 ml) and dried over anhydrous Na_2SO_4. GLC analysis indicated a yield of 90% of 2-octanone (ethylbenzene as an internal standard).

Oxidation of 3β-Cholestanol with Bromine Utilizing Bis(tributyltin) Oxide. A THF (20 ml) solution of 3β-cholestanol (379 mg, 0.975 mmol) and bis(tributyltin) oxide (1169 mg, 1.961 mmol) was heated at 50—60 °C in the presence of molecular sieves for 1 h. A THF (10 ml) solution of bromine (313 mg, 1.96 mmol) was then added drop by drop within a period of 30 min at room temperature. The reaction mixture was quenched with powdered $Na_2S_2O_3$ (1.0 g), stirred for 30 min and filtered. After concentration of the filtrate under reduced pressure, NH_4F (10 g) in water (10 ml) and ether (10 ml) were added to the remaining residue. The mixture was stirred for 30 min, and the resulting precipitate was filtered off. The ethereal layer was washed with removal of the solvent, 3-cholestanone (337 mg, 89%) was isolated by column chromatography (silica gel).

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