Organic Synthesis in Micellar Media. Oxidation of Alcohols and Their Conversion into Alkyl Chlorides

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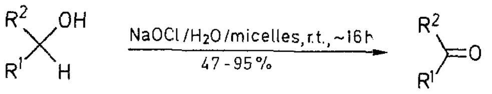
The use of micelles was investigated for various organic reactions: oxidation of alcohols with sodium hypochlorite in micelles, oxidation of alcohols with hexadecyltrimethylammonium chromate as micelle, and conversion of primary alcohols to 1-chloroalkanes by aqueous hydrogen chloride in the presence of micelles. In all cases, product isolation was simple and satisfactory yields were obtained.

One of the most important and most interesting aspects of the rapidly developing field of micellar chemistry is its application to organic synthesis. Reaction modeling of enzymatic processes is of interest in mechanistic studies, especially as regards the use of enzyme models for the hydrolysis of carboxylic esters in micellar systems.[1,2] Although the mechanism of micellar catalysis is well understood[3,4] the use of micelles in preparative chemistry is still limited. The advantage of large rate enhancement is offset by the limited substrate solubilization, the restricted temperature range, and the difficulty of separating the products from the surfactants.[5] In spite of these limitations, we now succeeded in elaborating a procedure for the convenient use of micelles in organic synthesis.[6-8]

The search for mild, versatile, and selective reagents for the operationally simple oxidation of alcohols to carbonyl compounds has been and still is the subject of many investigations. A large number of reagents containing or consisting of chromium(VI) ion,[9,10] manganese(IV) oxide,[11,12] potassium permanganate absorbed on a solid support,[13] and sodium hypochlorite[14-16] have been studied, but many of them do not meet the high requirements of modern organic synthesis, for example, as regards the oxidation or preparation of complexes of highly sensitive substrates. Of the chromium(VI) reagents which are widely used for the oxidation of primary and secondary alcohols to the corresponding carbonyl compounds,[17,18] Collins reagent [chromium(VI) oxide-pyridine complex] has the drawback that it has to be used in large excess (5-6 molecular equivalents), that it is unstable and hygroscopic, and that it is prepared by a dangerous procedure during which spontaneous ignition can occur.[19] The second widely used reagent, pyridinium chlorochromate, is prepared easily and safely by the addition of chromium(VI) oxide and hydrochloric acid to pyridine.[10,20] Pyridinium chlorochromate is slightly acidic and usually does not react with simple olefinic C=C bonds. The best reagent in this series is poly[vinyl(pyridinium chlorochromate)],[21] the reactions of which are very clean, combined with simple product isolation. Good yields of aldehydes and ketones have also been obtained by oxidation of alcohols with a solution of tetrabutylammonium chromate in chloroform.[22] One of the simplest chromium(VI) reagents is chromic acid absorbed on silica gel;[23] it is suitable for the oxidation of hydroxy compounds to carbonyl compounds.

The conversion of alcohols into alkyl chlorides can be achieved with several reagents, e.g., with hydrochloric acid or with inorganic acid halides such as thionyl chloride,[24] phosphorus(III) chloride, phosphorus(V) chloride, phosphoryl chloride,[25] etc. Tertiary chlorides are easily prepared with concentrated hypochloric acid, but the reaction of primary and secondary alcohols with aqueous hydrochloric acid is slow and a catalyst, usually zinc chloride, is required.[26,27] Treatment of primary alcohols with hydrochloric acid in the presence of hexamethylphosphoric triamide[28] or hexadecyltributylphosphonium bromide[29] under phase-transfer conditions gives 1-chloroalkanes in good yields.

We report here the high effectiveness of aqueous sodium hypochlorite in the presence of micelle which makes this readily available and inexpensive reagent equal if not even superior to other special reagents for the oxidation of many alcohols. Arylcarbinols and secondary alcohols are smoothly converted to carbonyl compounds by stirring, at room temperature, an excess of 4% aqueous sodium hypochlorite (commercial swimming pool bleach) with a solution of the substrate in aqueous sodium dodecyl sulfate, sodium stearate, or hexadecyltrimethylammonium bromide as a micelle. In the absence of micelles, little or no reaction is observed and the alcohol is recovered unchanged (Table 1).



Primary aliphatic alcohols are oxidized at a relatively slow rate to the corresponding aldehydes which, in contrast to aromatic aldehydes, usually are very rapidly oxidized to carboxylic acids. Some secondary carbinols can also be oxidized with sodium hypochlorite in the presence of the micelle and ammonium chloride (Table 1). The best yields of carbonyl compounds were obtained when 2 equivalents of oxidant were used (with 1.1 equivalents of oxidant an only 35% yield of ketone was obtained in one case).

Table 1. Carbonyl Compounds Obtained by Oxidation of Alcohols with Sodium Hypochlorite in the Presence of Micelles

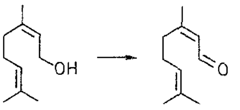
R^1	R^2	Micelle[a]	Yield (%)[b]
C_6H_5	H	SS	90
		SDS	90
		CTAB	87
C_6H_5	C_6H_5	SS	95
		SDS	92
c-C_6H_{11}	H	SDS[c]	55
		CTAB[c]	58
C_2H_5	CH_3	SS[c]	47
		SDS[c]	49
		CTAB[c]	52

[a] SS: Na stearate; SDS: Na dodecyl sulfate; CTAB: Hexadecyltrimethylammonium bromide (nonproprietary name: cetyltrimethylammonium bromide).

[b] Yield of isolated product.

[c] Reaction carried out in the presence of NH_4Cl.

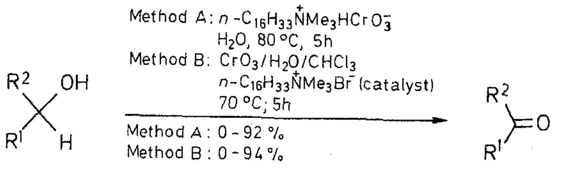
Table 2. Oxidation of Alcohols with Hexadecyltrimethylammonium Chromate (Method A) or with Chromium (VI) Oxide in the Presence of Hexadecyltrimethylammonium Bromide as Phase-Transfer Catalyst (Method B)

R^1	R^2	Yield (%)[a] Method A	Method B
C_6H_5	H	87	85
C_6H_5	C_6H_5	92	94
3-pyridyl	H	83	81
4-pyridyl	H	85	81
C_2H_5	CH_3	42	45
$PhOCH_2$	H	–[b]	–[b]
$PhOCH_2CH_2OCH_2$	H	–[b]	–[b]
		82	84

[a] Yield of isolated product; purity: ~98% (GLC). The IR and ^1H-NMR spectra were identical with those of authentic specimens.

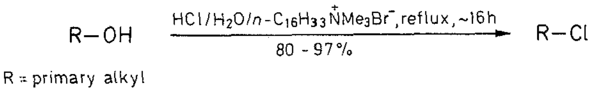
[b] The starting alcohol was quantitatively recovered.

The second reagent used for the oxidation of alcohols to carbonyl compounds was hexadecyltrimethylammonium chromate which, as micelle in aqueous solution or under phase-transfer conditions, is remarkably effective and simple to handle. This salt is easily and safely prepared by the addition of hexadecyltrimethylammonium bromide to an aqueous solution of the equimolecular amount of chromium(VI) oxide. The immediately formed yellow-orange precipitate can be isolated and used for the oxidation of alcohols in aqueous solution (the isolated salt is a surfactant), e.g., for the oxidation of benzyl alcohol to benzaldehyde in 87% yield (Method A).



A second possibility is the direct use of the suspension of hexadecyltrimethylammonium chromate, without isolation of the oxidizing agent. Since both procedures lead to essentially the same results, the isolation step was omitted in all reactions described here. In a typical procedure, 4 mmol of benzyl alcohol was oxidized with an excess (1 : 2.5 mole ratio) of hexadecyltrimethylammonium chromate at 80 °C. After 5–10 hours, the reaction mixture was cooled and worked up to give benzaldehyde in 87 % yield. The same result was obtained when the reaction was carried out at room temperature for 50 hours (Table 2). Primary aliphatic alcohols are oxidized at a slow rate to aldehydes which, in contrast to aromatic aldehydes, usually are oxidized very rapidly to the corresponding carboxylic acids. An attempt was made to apply this oxidation to a two-phase system with hexadecyltrimethylammonium ion as phase-transfer catalyst. It was evident that under these conditions the presence of the onium salt plays an important role in accelerating the reaction; depending on the starting alcohol and the reaction temperature, an overall 20–50 % increase in yield of carbonyl compound was achieved (Method B). Thus, for example, the oxidation of 4 mmol of benzyl alcohol with 10 mmol of chromium(VI) oxide in a two-phase system (water/chloroform) in the presence of 2 mmol of hexadecyltrimethylammonium bromide at 70 °C gave benzaldehyde in 85 % yield, in contrast to a 41 % yield obtained without hexadecyltrimethylammonium bromide. The application of phase-transfer catalysis to this reaction improved the procedure notably.

In order to improve the yields in the conversion of primary alcohols to alkyl chlorides with hydrochloric acid, the reactions were performed in the presence of hexadecyltrimethylammonium bromide and hexadecylpyridinium bromide (cetylpyridinium bromide, CPB) as micelles. In the absence of micelles (surfactants), the reaction of water-soluble primary alcohols with hydrochloric acid afforded the corresponding 1-chloroalkanes in up to 60 % yields whereas with water-insoluble primary alcohols the yields were only ~ 30 %. Micelles have a favorable effect on the solubility of the primary alcohols in concentrated hydrochloric acid, so that under micellar conditions primary alcohols were converted into 1-chloroalkanes in 90–97 % yields (Table 3). Generally, 2.5 mol of concentrated hydrochloric acid and 0.0025 mol of surfactant per 0.1 mol of primary alcohol were used, because no significant increase in reaction rate or yield was observed when 0.00025 mol of surfactant was employed (the concentration of surfactant was below the critical micellar condition).



$$\text{R–OH} \xrightarrow[80-97\,\%]{\text{HCl}/H_2O/n\text{-}C_{16}H_{33}\overset{+}{N}Me_3Br^-,\ \text{reflux},\ \sim 16\,\text{h}} \text{R–Cl}$$

R = primary alkyl

In the absence of micelle, the exchange is much slower and a maximum conversion of 70 % was achieved after 70 hours. It was observed that in the presence of a surfactant the chain length has no noticeable effect on the rate and yield of conversion. GLC and ^{1}H-NMR analysis showed that no dialkyl ethers or isomeric chloroalkanes were formed. The experimental data suggest that the reaction takes place in the micelle, where chloride ion is transferred by the surfactant. In this medium, anions are especially reactive both because of their relatively low energy of interaction with the complex cation or surfactant, and because of poor solvation, which favours S_N2 displacement.

The products were 96 % pure as determined by GLC, IR, and ^{1}H-NMR analysis (GCL conditions: 10 % carbowax 20 M on 60–80 mesh chromosorb (W).

Table 3. Conversion of Primary Alcohols into 1-Chloroalkanes using 37 % Hydrochloric Acid in the Presence of Micelles

Product	Yield (%) of 1-Chloroalkane		
	Surfactant		
	Hexadecyl-trimethyl-ammonium Bromide	Hexadecyl-pyridinium Bromide[a]	None
n-C_4H_9Cl	80	81	61
n-$C_6H_{13}Cl$	85	86	54
n-$C_8H_{17}Cl$	87	91	47
n-$C_{10}H_{21}Cl$	95	91	42
n-$C_{12}H_{25}Cl$	97	95	35
n-$C_{14}H_{29}Cl$	93	91	30
n-$C_{16}H_{33}Cl$	90	92	31
$C_6H_5CH_2CH_2Cl$	87	83	41

[a] Nonproprietary name: Cetylpyridinium bromide (CPB).

The simplicity and low cost might render the present method a preferable alternative to existing procedures for the conversion of alcohols to carbonyl compounds[10,14–23] and of primary alcohols to 1-chloroalkanes.[24–27]

The alcohols used as substrates were purchased and, where necessary, purified before use. Commercially available (Fluka) hexadecyltrimethylammonium bromide was used without further purification.

Analytical GLC was performed on a Varian Model 920 gas chromatograph with standard Carbowax 20 M columns. Melting points were determined on a Kofler hot-stage microscope apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 grating infrared spectrophotometer using standard liquid film and Nujol mull techniques. Nuclear magnetic resonance spectra were recorded on a JEOL FXQ spectrometer. The products were identified by comparison of their physical data and their IR and NMR spectra with those of commercial samples. In all cases, the analytical and spectral data of the products were consistent with the assigned structures.

Oxidation of Benzyl Alcohol with Sodium Hypochlorite in Sodium Stearate Micelle; Typical Procedure:

Benzyl alcohol (1.06 g, 0.01 mol) is dissolved in a 0.02 molar aqueous solution of sodium stearate (500 mL). This solution is stirred at room temperature, 4 % aqueous NaOCl solution (35 mL, 0.02 mol) is added, and stirring is continued overnight. The mixture is then saturated with NaCl. The aqueous layer is filtered and extracted with Et_2O (3 × 100 mL). The extract is dried (Na_2SO_4) and evaporated under reduced pressure to leave a semisolid mixture containing sodium stearate. Purification by column chromatography on a silica gel column with hexane as eluent affords benzaldehyde; yield: 0.95 g (90 %), colorless oil; purity: 99 % (GLC).

Hexadecyltrimethylammonium Chromate:

To a stirred solution (20 mL) of CrO_3 (1.0 g, 10 mmol) in H_2O (20 mL), a solution of hexadecyltrimethylammonium bromide (3.64 g, 10 mmol) in H_2O (500 mL) is rapidly added at room temperature. A yellow-orange solid precipitates immediately. The mixture is cooled to 0 °C. The resulting solid product is collected on a sintered-glass funnel, washed carefully with cold H_2O (35 mL), dried under vacuum, and stored over $CaCl_2$; yield: 3.21 g (80 %).

Oxidation of Benzyl Alcohol with Hexadecyltrimethylammonium Chromate Under Micellar Catalysis (Method A); Typical Procedure:

To a stirred suspension of hexadecyltrimethylammonium bromide (3.64 g, 10 mmol) and CrO_3 (1.0 g, 10 mmol) in H_2O (500 mL) benzyl alcohol (0.43 g, 4 mmol) is added at room temperature. The suspension is heated at 80 °C for 5 h, then saturated with NaCl, and filtered. The filtrate is extracted with Et_2O (3 × 100 mL), and the extract is dried (Na_2SO_4). The solvent is removed under reduced pressure to leave a deep-red semisolid mixture containing hexadecyltrimethylammonium chromate. This mixture is filtered with Et_2O through a column of silica gel. The filtrate is evaporated. The resultant crude product (0.4 g, 95% purity as determined by GlC, 97% yield) is further purified by column chromatography on silica gel using hexane as eluent to afford colorless benzaldehyde; yield: 0.36 g (87%); purity: 98% (GLC).

Oxidation of Benzyl Alcohol with Chromium(VI) Oxide under Phase-Transfer Catalysis (Method B); Typical Procedure:

To a stirred suspension of hexadecyltrimethylammonium bromide (0.72 g, 2 mmol) and CrO_3 (1.0 g, 10 mmol) in H_2O (500 mL), a solution of benzyl alcohol (0.43 g, 4 mmol) in $CHCl_3$ (100 mL) is added at room temperature, the mixture is heated at 70 °C for 5 h, then cooled to room temperature, and saturated with NaCl. The mixture is filtered, and the filtrate is extracted with Et_2O (2 × 100 mL). The combined organic phases are dried (Na_2SO_4), and the solvent is removed by rotary evaporation to give the crude product which contains hexadecyltrimethylammonium chromate. Purification is carried out in the same way as in Method A; yield: 0.35 g (85%).

1-Chlorooctane from Octanol; Typical Procedure:

A mixture of octanol (13 g, 0.1 mol), hexadecyltrimethylammonium bromide (1 g, 0.0025 mol) and 37% aqueous HCl (205 mL, 2.5 mol) is heated at reflux temperature overnight. After cooling, the organic layer is separated, and the aqueous phase is extracted with petroleum ether (3 × 100 mL). The combined organic layers are washed with 10% aqueous Na_2CO_3 (50 mL) and dried (Na_2SO_4). The solvent is removed under reduced pressure to leave an oil (containing surfactant) which is partially separated by filtration with Et_2O through a column of silica gel. The filtrate is evaporated, and the oily residue (14 g) is distilled under reduced pressure to give 1-chlorooctane; yield: 13 g (87%); bp 95–98 °C/18 Torr; purity: 96% (GLC).

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