Oxidation of Primary Alcohols to Methyl Esters Using *tert*-Butyl Hypochlorite, Pyridine and Methyl Alcohol

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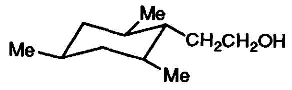
When treated with *tert*-butyl hypochlorite, in the presence of pyridine and methyl alcohol, saturated aliphatic primary alcohols are oxidized to methyl esters in very high yields. Oxidation of benzylic alcohols, under the same conditions, yields a mixture of aldehydes and methyl esters. It appears that this reaction is a three-step process with an aldehyde and acyl chloride as the intermediates. Investigation of the relative rates of reaction reveals that benzyl alcohols are, as expected, oxidized faster than aliphatic alcohols, while the corresponding aldehydes show an opposite trend in reactivity. The reaction mechanism is proposed and the difference in the reactivity for aliphatic and benzylic aldehydes attributed to the stereoelectronic factors.

Primary alcohols can be oxidized to the alkyl esters of the corresponding carboxylic acids by many oxidizing agents including *tert*-butyl hypochlorite or *N*-chlorosuccinimide in the presence of pyridine,[1] oxygen and cobalt salts,[2] *N*-bromosuccinimide,[3] chromic acid[4] or sodium and calcium hypochlorite,[5] but the direct conversion of primary alcohols into methyl esters has been achieved only by oxidation with manganese dioxide in methyl alcohol.[6]

In our previous paper[7] we reported that *tert*-butyl hypochlorite in the presence of pyridine (TBHC–Py) is a very good reagent for the oxidation of saturated acyclic, cyclic and benzylic secondary alcohols to ketones. In the course of our investigation of this oxidation method, we have discovered that TBHC–Py in the presence of methyl alcohol can be employed for the oxidation of primary alcohols to the methyl esters of the corresponding carboxylic acids in a simple, one-step, one-pot reaction (Scheme 1). We used saturated primary aliphatic and benzylic alcohols containing no other functional groups. The results are presented in Table 1. For oxidation in methylene dichloride the proportion of reactants was two moles of pyridine and five moles of methyl alcohol per mole of alcohol used for oxidation; after mixing the components at room temperature oxidation is complete in *ca.* 3 h. Following the usual work-up,[7] yields were determined and products identified by GC–MS, except in the cases where the ester was isolated by distillation and the products identified by IR spectroscopy. The yield of methyl esters from aliphatic alcohols is very high and besides alkyl esters the only other reaction products were *tert*-butyl alcohol, pyridine hydrochloride and some unchanged starting alcohol, except in the case of 2-(*t*-2,*t*-4,*t*-6-trimethylcyclohexan-*r*-1-yl)ethanol (**1**) where a small amount of aldehyde is observed. Unfortunately the procedure described, even when modified, cannot be applied to the preparative synthesis of aliphatic aldehydes. Oxidation of one mole of pentan-1-ol using one mole of TBHC–Py and five moles of methyl alcohol produces no aldehyde at all, but the usual mixture of products with 50% of unchanged starting alcohol.

$$RCH_2OH \xrightarrow{i} RCO_2Me + Py{\cdot}HCl + Bu^tOH$$

Scheme 1 *Reagents and conditions:* i, TBHC–Py, MeOH, CH_3Cl, 5 °C



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On the other hand, using benzylic alcohols, aldehydes are the predominant products, especially when the benzene ring is substituted with an electron-withdrawing group. All benzylic aldehydes appear to be quite stable under the reaction conditions; GC analysis of the reaction mixture produced when *p*-methylbenzyl or benzyl alcohol was oxidized, showed that the yields and ratios of aldehyde and methyl ester did not change when an excess (25%) of TBHC–Py was used.

Methyl alcohol is also oxidized by this method, but very slowly; the mixture of TBHC–Py and methyl alcohol in methylene dichloride, in the ratio normally applied for oxidation of primary alcohols, lost oxidizing power after 12 h. Although no attempt to investigate this reaction mixture has been made, it has been shown to contain *tert*-butyl alcohol, formaldehyde and methyl formate by GC–MS.

The reaction is also sensitive to oxygen. The rate of oxidation of pentan-1-ol, followed iodometrically, was significantly retarded when oxygen was continually introduced to the reaction mixture. Evaporation of the solvent left a brown oily residue which was not investigated. In contrast when the reaction is carried out under purified argon (alkaline pyrogallol) the reaction rate and products for oxidation of pentan-1-ol, were not different from the rate and products observed under the conditions usually applied.

An additional interesting result is formation of cyclohexyl chloride when cyclohexane is present in the reaction mixture; thus oxidation of nonan-1-ol in the presence of an equimolar amount of cyclohexane produces 50% of methyl ester and 50% unchanged starting alcohol (yields based on nonan-1-ol) together with 50% of cyclohexyl chloride (yield based on cyclohexane).

From a mechanistic point of view this reaction is thought to proceed as indicated in Scheme 2. In the first step primary

$$RCH_2OH \xrightarrow{-H^-} RCH\text{–}OH \xrightarrow{-H^+} RCHO \xrightarrow{-H^{\cdot}} RC{=}O \xrightarrow{i}$$
$$RCOCl \xrightarrow{ii} RCO_2CH_3$$

Scheme 2 *Reagents:* i, TBHC or Cl_2; ii, MeOH

Table 1 Oxidation of primary alcohols with TBHC–Py in the presence of methyl alcohol

Alcohol	ROH (mmol)	TBHC (mmol)	Py (mmol)	MeOH (mmol)	CH_2Cl_2 (cm^3)	Yield of products (%)[a,c] A	B	C	D
Pentan-1-ol[b]	113	230	230	570	230	82	9	7	—
Heptan-1-ol[b]	26	55	55	130	80	80	10	9	—
Nonan-1-ol	34	70	70	170	200	100	—	—	—
Decan-1-ol	10	20	20	50	90	99	—	—	—
Tetradecan-1-ol	6	12	12	30	30	90	—	7	—
Cyclohexylmethanol	26	52	52	30	40	100	—	—	—
Cyclopentadecylmethanol	5	10	10	30	40	100	—	—	—
$RC_6H_{10}OH$									
R = *cis*-4-Bu^t	5	11	11	30	40	95	—	5	—
R = *trans*-4-Bu^t	5	11	11	30	40	95	—	6	—
trans-2-(*cis,cis,cis*-$R_3C_6H_8$)CH_2CH_2OH									
R = 2,4,6-Me	3	6	6	20	30	92	—	7	0.4
p-$XC_6H_4CH_2OH$									
X = H[b]	92	190	190	450	250	30	—	—	62
X = Cl	10	20	20	50	90	15	—	—	81
X = Me	11	22	22	50	90	19	—	—	63

[a] Calculated from GC using chlorobenzene as internal standard unless otherwise stated. [b] Ketone isolated by distillation. All yields based on starting alcohol. [c] A = RCO_2CH_3; B = RCO_2CH_2R; C = RCH_2OH; D = RCHO.

alcohol is oxidized to aldehyde. The relative reactivities, measured by the rate of disappearance of alcohol show that benzylic alcohols react faster with TBHC–Py than do aliphatic alcohols and the following reactivities were observed: benzyl alcohol:*p*-chlorobenzyl alcohol:pentan-1-ol:ethyl alcohol 2.60:1.75:1.00:1.00, indicating the hydride breaking of α-C–H bond and participation of the aromatic ring in the transition state. The same mechanism was proposed for oxidation of secondary alcohols with TBHC–Py.[7]

In the next step the aldehyde undergoes further oxidation to acyl chloride, possibly by a radical chain mechanism, involving breaking of aldehydic C–H bond and formation of acyl radical, which in turn reacts with a chlorine atom donor in the form of TBHC or molecular chlorine formed by TBHC oxidation of chloride ion.[8] The reaction of aldehyde with TBHC is known to produce acyl chloride, and recently a modification has been reported as a convenient synthetic route for methyl esters from aldehydes.[10] The acyl chloride can be isolated if the oxidation is performed without methyl alcohol and by addition of a primary alcohol to the solution of TBHC–Py in methylene dichloride; thus hexan-1-ol treated with two moles of TBHC–Py produces 60% of hexanoyl chloride (40% of hexyl ester of hexanoic acid) which can be isolated or converted into the ethyl ester by addition of ethyl alcohol to the reaction mixture. Investigation of the relative rate of the reaction of aldehydes with TBHC–Py shows that benzylic aldehydes are less reactive than aliphatic aldehydes; the competitive experiments indicated relative reactivities, pentanal:*p*-chlorobenzaldehyde 2.15:1.00, pentanal:benzaldehyde 1.90:1.00 and pentanal:*p*-methylbenzaldehyde 1.35:1.00. Similar unexplained higher reactivity of aliphatic aldehydes is observed in some other reactions, such as autoxidation,[11] decarbonylation of aldehydes in the presence of benzyl thiol,[12] reaction of aldehydes with pure TBHC[13] or trichloromethyl radical,[14] where the aldehydic C–H bond is broken by radical mechanism. The observed order of the reactivity is the reverse of the expected order if the stabilities of the intermediate acyl radicals are compared, since the acyl radical should be better stabilized by an adjacent phenyl than the alkyl group, but the radical breaking of the aldehydic C–H bond may be the case where the factors stabilizing the intermediate do not stabilize the transition state. We believe that in this case stereoelectronic factors control the rates of the reaction. While in the aliphatic aldehyde the formyl group can freely rotate around the C_1–C_2 bond, a benzaldehyde has one conformation of the lowest energy; *i.e.* when the π-orbital of the carbonyl group is in maximum overlap with the π-electron system of the benzene ring. In this conformation all the constituent atoms (including the aldehydic hydrogen) of the benzaldehyde lie in the same plane and the aldehydic C–H bond is perpendicular to the plane in which the π-orbital of the carbonyl group is situated. The breaking of this bond probably has a transition state of the same geometry where participation of π-electrons of the benzene ring is not possible since the C–H bond is not properly oriented. In the aliphatic aldehyde, on the other hand, stereoelectronic factors play no part in the transition state and the inductive and hyperconjugative effects control the rate of the reaction. However, this provides a strictly *ad hoc* explanation and the problem of the control of this reaction invites further study.

Experimental

Gas Chromatography.—A Perkin-Elmer 3920 B instrument (flame ionization detector) was used for analytical purposes and a Varian Aerograph 920 instrument (thermistor detector) for preparative separations. The columns (2 m × 2 mm analytical; 2 m × 4 mm preparative) consisted of Carbowax 20M on Chromosorb W (3% analytical; 10% preparative); the carrier gas was H_2 or Ar.

Instrumentation.—IR spectra were recorded using a Perkin-Elmer model 197 instrument, NMR spectra using a Varian spectrometer FT-80A and GC–MS spectra using Finnigan MAT mass spectrometer Model 8230.

Reagents.—Solvents and reactants were either commercially available or synthesized by well established methods. Their physical constants were checked and in general their purity confirmed by GC, IR and NMR spectroscopy.

Oxidation of Primary Alcohols.—All experiments on a larger scale were carried out in a flask equipped with a magnetic stirrer, dropping funnel and condenser. The alcohol, pyridine and methyl alcohol were placed into the flask together with calculated amount of methylene dichloride, so that the concentration of both pyridine and alcohol was 0.1–0.2 mol dm^{-3}, and the concentration of methyl alcohol 0.5–1.0 mol dm^{-3}. Two equimolar amounts of *tert*-butyl hypochlorite were added over

1 min and the mixture stirred for 1 h in an ice-bath. The mixture was then washed with aqueous potassium iodide and sodium thiosulphate (if necessary), diluted with hydrochloric acid and aqueous sodium hydrogencarbonate. After drying (Drierite), the mixture was distilled over an efficient column, the methyl ester was collected and identified by IR and NMR spectroscopy. When working with small amounts of alcohol the yields of methyl esters and other products were determined by GC–MS and GC using an internal standard added before reaction.

Relative-rate Determinations.—These were carried out in a small flask equipped with magnetic stirrer, dropping funnel and condenser, immersed in a constant-temperature bath (20.5 °C). The solution of the two alcohols or aldehydes (0.1 mol dm^{-3} each) and pyridine (0.1 mol dm^{-3}) in methylene dichloride was placed in the flask, together with an internal standard (chlorobenzene). *tert*-Butyl hypochlorite (one half of the equimolar amount) was added in one portion and the mixture stirred for 1 h. After washing with potassium iodide, sodium thiosulphate, dilute hydrochloric acid, sodium hydrogencarbonate and drying, the mixture was analysed by GC and the relative reactivities were determined using the relation $(\log A/A_0)/(\log B/B_0) = r$, where A_0 and B_0 are the peak areas of the two alcohols relative to that of the internal standard prior to reaction and A and B the quantities after reaction.

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