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Remarkable reactivity of pyridinium chlorochromate adsorbed on neutral alumina under solvent-free conditions

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Dedicated to Professor B. C. Ranu on the occasion of his 53rd birthday

Abstract—Pyridinium chlorochromate adsorbed on neutral alumina (PCC-Al_2O_3) under solvent-free conditions has been found to oxidize primary aliphatic alcohols to alkyl alkanoates whereas primary benzylic and primary allylic alcohols produce the corresponding aldehydes. Secondary aliphatic and aromatic alcohols produce ketones without isomerization and polymerization of double bonds, overoxidation and other side-reactions. © 2003 Elsevier Science Ltd. All rights reserved.

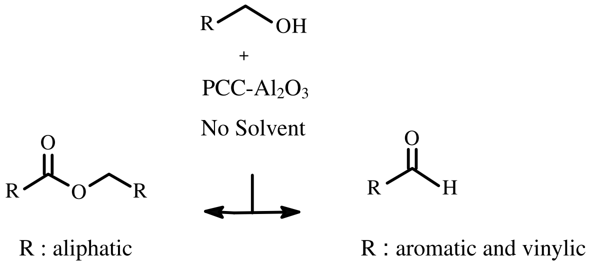
1. Introduction

Oxidation of alcohols to carbonyl compounds is one of the most fundamental reactions in organic chemistry.[1] Many effective reaction systems have been developed using stoichiometric chromium(VI) salts[2] of which PCC[3a] has drawn much attention for many useful synthetic transformations.[3b] However, the utility of the chromium reagents is compromised by their inherent toxicity, potential danger (ignition or explosion of some reagents) and difficulties in terms of product isolation and waste removal due to contamination with Cr(III) by-products. To overcome some of these problems PCC-Al_2O_3 has been utilised for the oxidation of various primary and secondary alcohols to the corresponding aldehydes and ketones in various organic solvents[4] such as benzene and dichloromethane. However, most organic solvents are high in the list of toxic and otherwise damaging compounds. Nowadays economical and environmental pressures are forcing the chemical community to search for more efficient ways of performing chemical transformations in a single operation by reusable catalysts avoiding toxic and costly reagents, large amounts of solvents and expensive purification techniques.[5] Reactions using solid-supported reagents and scavengers have created considerable interest among synthetic chemists around the world.[6] Due to several advantages in terms of yield, purity and selectivity, supported reagents have been used under solvent-free conditions for the synthesis[7] of various important synthetic intermediates. As a part of our effort to develop[8] new methodologies in economically viable and environmentally benign conditions we report herein a very simple oxidative protocol using PCC-Al_2O_3 at room temperature in the absence of any solvent with novel findings and greater advantages over the conventional PCC oxidations in various organic solvents.

2. Results and discussion

At the outset, a number of aliphatic, aromatic and benzylic primary alcohols were subjected to oxidative transformation with PCC-Al_2O_3 in the absence of solvent to give some new results, presented in Scheme 1. Quite interestingly, several constitutionally varied aliphatic primary alkanols[9] gave the corresponding alkyl alkanoates[10] under solvent-free conditions without a detectable (by 300 MHz ^1H NMR) trace of the aldehydes, whereas, benzylic primary alcohols[9] (unsubstituted, substituted and vinylogous), under the same oxidative condition produced the corresponding aldehydes without further oxidation to the corresponding carboxylic acids or ester. Detailed results are provided in Table 1.

As shown in Table 1, various alkyl alkanoates[10] having diverse substitution patterns were obtained directly in one-pot from the corresponding aliphatic primary alkanols[9]



Scheme 1.

Keywords: oxidation; supported reagents; solid-phase synthesis.

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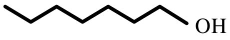
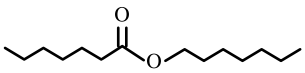
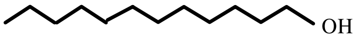
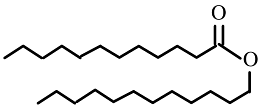
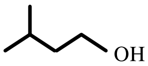
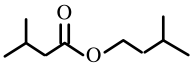
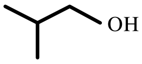
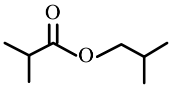
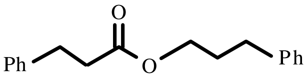
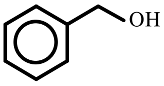
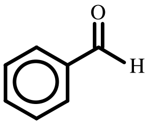
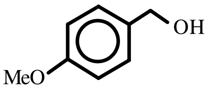
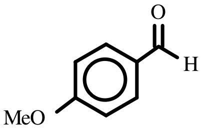
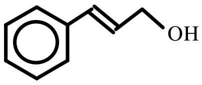
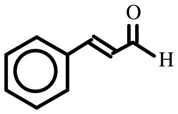
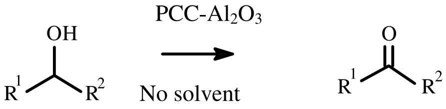
Table 1. Oxidation of primary alcohols[9a] using PCC on Al_2O_3 under solvent-free conditions

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1		3		71[10a]
2		3		82[10b]
3		3		65[10c]
4		4		68[10d]
5		3		76
6		1		82[9]
7		1		82[9]
8		1		70[b][9]

[a] Yield refers to the purified products; fully characterised chemically and spectroscopically.
[b] Benzaldehyde (15%).

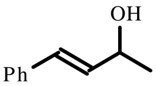
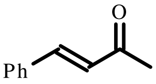
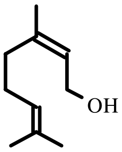
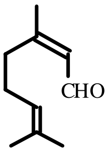
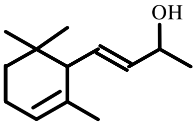
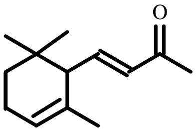
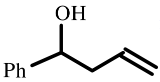
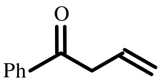
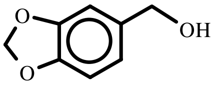
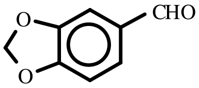
under the said solvent-free oxidative conditions in fairly good yield and high purity (entries 1–5 in Table 1). Unsubstituted, substituted and vinylogous benzylic primary alcohols[9] underwent oxidation under similar conditions to produce the corresponding aldehydes in high yield without being further oxidized to the corresponding carboxylic acids or esters (entries 6–8 in Table 1), presenting remarkable selectivity of this solvent-free oxidative protocol in contrast to the reported methods[4] using PCC-Al_2O_3 in an organic solvent (which lead to the formation of the corresponding aldehydes from both aliphatic and benzylic primary alcohols). Alkyl alkanoates having varied molecular skeletons are very important due to their occurrence as various natural products [e.g. isopentyl isovalerate[10c] (entry 3 in Table 1) is an essential constituent in the Japanese peppermint oil, Shubi] and they find useful applications in the perfumery industry[10b] as well as in synthetically important telomerization reactions[10d] with various olefins and forming multimolecular films[10b] having important interfacial properties. The same methodology has been applied to a number of structurally varied alcohols,[9] as delineated in Scheme 2; the results of which are presented in Table 2.



Scheme 2.

As is evident from Table 2, structurally varied saturated aliphatic acyclic (entries 1,2), aryl alkyl (entries 3–5), diaryl (entry 6), alicyclic (entry 7) and benzo-fused (entry 8) secondary alcohols[9] underwent clean oxidation to the corresponding ketones at ambient temperature within a reasonable period of time on the surface of neutral alumina impregnated with PCC in absence of any solvent in good yield and high purity. This can be attributed mainly to the

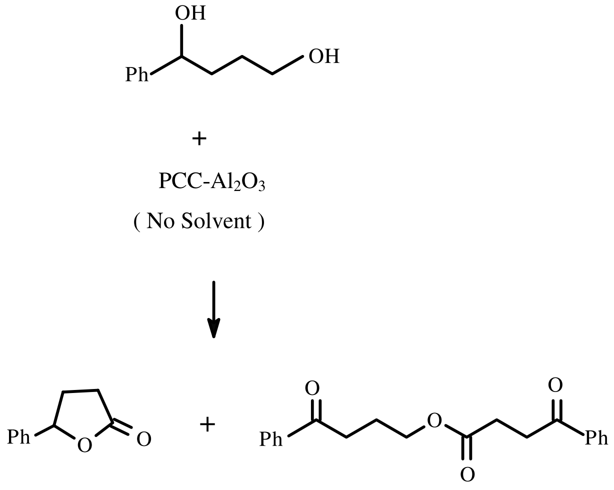
Table 2. Oxidation of alcohols[9,17] using PCC on Al_2O_3 under solvent-free conditions

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	4-Methyl-2-pentanol	24	4-Methyl-2-pentanone	83[9]
2	1,3-Diphenylpropan-2-ol	20	Dibenzyl ketone	84[9]
3	1-Phenyl-1-propanol	2	Propiophenone	82[9]
4	1-(4-Chlorophenyl)ethanol	4	4-Chloroacetophenone	79[9]
5	1-(4-Methoxyphenyl)-1-ethanol	20	4-Methoxyacetophenone	88[9]
6	Benzhydrol	2	Benzophenone	81[9]
7	4-*t*-Butylcyclohexanol	2	4-t-Butylcyclohexanone	89[9]
8	1-Tetralol	2.5	1-Tetralone	93[9]
9	Benzoin	24	Benzil	75[9]
10	1,2-Diphenylethane-1,2-diol	36	Benzil	56[9]
11	4-Methylpent-3-en-2-ol	14	4-Methylpent-3-en-2-one	78[9]
12		2		75[9c]
13		2		83[9]
14		2		85[9]
15	 [18]	2		72[19]
16		2		82[9]

[a] Yield refers to the purified products; fully characterized chemically and spectroscopically.

immobilization of the Cr-containing by-products on the alumina support.[11] The notable feature of the said methodology is the elimination of several side-reactions which are often associated with various conventional oxidative methods using higher valent metals as oxidants.[12] Over oxidation of alkyl benzyl ketone to 1,2-diketone, benzaldehyde and benzoic acid (which is a common phenomenon[13] using PCC and pyridine in dichloromethane) is completely eliminated in the present methodology (entry 2 in Table 2). 1,2-Diols and α-hydroxyketones have been reported to undergo oxidative cleavage[14] of the C–C bond with PCC in dichloromethane, but the said substrates under the present solvent-free conditions cleanly produce the desired oxidation products, namely, 1,2-diketones in appreciable yield without much formation of side-products (entries 9,10 in Table 2). Allylic primary and secondary alcohols smoothly underwent oxidation in the present condition to the corresponding α,β-unsaturated aldehydes and ketones in fairly good yield and purity without polymerization of the olefinic linkage (entries 11–14 in Table 2). Another very important advantage of the said methodology is that the isolated double bonds remain unaffected under the present conditions (entries 13–15 in Table 2). Even no isomerization of the isolated double bonds to the more stable conjugated ones in the oxidation products was observed (entries 14,15 in Table 2). Acid-labile groups are compatible with this reagent system as is evident from the complete survival of the methylenedioxy moiety (entry 16 in Table 2) during the reaction. Neutral alumina, due to its amphoteric nature, probably attenuates the acidity of the medium to such a level which is insufficient to cause acid-catalyzed transformations of the sensitive moieties. Alumina recovered after the reaction can be recycled with minor variation of yield after washing with acid, neutralization and activation. Cr(III) salts in the mother liquor obtained after washing can be oxidized to chromate which can be used as oxidants. Thus, the said oxidative method under solvent-free conditions has set out to minimize the dispersion of offensive materials in the environment and maximize the use of renewable resources. From this standpoint this solid phase method can be considered as a relatively green technology having more advantages and wider applicability compared to the conventional PCC-oxidation methods in solution phase. The yields of the products are, in general, good. In some cases lower yields were obtained as the loss of the products could not be avoided during the isolation process due to highly volatile nature of the products (entries 3 and 4 in Table 1). Sometimes the products were contaminated (as detected by ^{1}H NMR) with starting materials after initial isolation (for examples, entries 1,5 in Table 1 and entries 9, 10,12,15 in Table 2), which were further purified by filtration chromatography over a short plug of silica gel or neutral alumina using hexane as eluent. Some unidentified by-products were formed (to the extent of nearly 10% by ^{1}H NMR) in a few cases (entries 10,12,15 in Table 2) which were removed by column chromatography.

The present solvent-free oxidative protocol using PCC-Al_2O_3 can thus serve as an excellent analogue of the celebrated Tishchenko reaction[15] for the one-pot synthesis of structurally varied alkyl alkanoates of wide applicability[10] from non-conjugated primary alkanols, instead of using aldehydes as the substrate. The reactions, at first sight, seem to be Tishchenko reaction catalyzed by Al(III) (from alumina) of the aldehydes produced by the initial oxidation of the primary alkanols by Cr(VI) reagent. But, PCC-Al_2O_3 under solvent-free conditions was unable to transform decanal to decyl decanoate even beyond the stipulated period of time; the aldehyde was recovered unchanged along with some polymeric products. This observation possibly suggests that the aldehyde may not be the actual intermediate in this transformation. PCC, without alumina, in the absence of solvent, yielded heptyl heptanoate (although in a lesser amount) from 1-heptanol along with some heptanal (to the extent of 5%) and some other unidentified by-products. Interestingly, no such oxidation of primary alkanol under the same solvent-free conditions was noted using either PDC alone or PDC-Al_2O_3 in place of PCC; 1-heptanol was recovered completely unaffected even after eight hours. Therefore, it seems that the reagent PCC is responsible for this unique transformation of primary alkanols to the corresponding alkyl alkanoates under solvent-free conditions; alumina serves as an effective matrix by attenuating the acidity of the medium and ensuring uniform exposure of the substrates to the reagents adsorbed in its pores, thereby decreasing the formation of the side-products to a great extent. The reaction probably takes place via the initial formation of the chromate ester intermediate which is rapidly oxidized to the alkanoate chromate mixed anhydride followed by nucleophilic attack of the unreacted alcohol leading to the formation of alkyl alkanoate. In the case of conjugated and aryl alcohols, the initially formed chromate ester takes up the usual oxidative route to the corresponding aldehydes which get some stabilization due to extended conjugation. Quite surprisingly, 2-phenylethanol yielded the corresponding alkyl alkanoate to a negligible extent under the present conditions; instead it was converted to benzaldehyde (53%), and the remainder was unreacted substrate. Presumably, the initially formed chromate ester underwent β-elimination to give a conjugated species, namely styrene; followed by the oxidative cleavage of the olefinic linkage forming benzaldehyde. The formation of benzaldehyde (to the extent of 15%) in the case of cinnamyl alcohol may also be attributed to this type of oxidative cleavage of the styrenic double bond. It is also interesting to note that when both alkyl and aryl alcoholic groups are present in the same molecule, the alkyl alcohol undergoes much faster oxidation than the aryl one, as evident from the fact that the oxidation of 1-phenylbutane-1,4-diol[16] using excess PCC-Al_2O_3 (>4 equiv.) under solvent-free condition produced 4-phenylbutan-1,4-olide (60% by ^{1}H NMR) along with the normal oxidation product, delineated in Scheme 3.



Scheme 3.

3. Conclusion

The present surface-mediated solid-phase procedure using pyridinium chlorochromate adsorbed on neutral alumina (PCC-Al_2O_3) under solvent-free conditions has been found to oxidize selectively primary aliphatic alcohols to alkyl alkanoates whereas primary benzylic and primary allylic alcohols produce the corresponding aldehydes. Secondary aliphatic and aromatic alcohols produce ketones without isomerization and polymerization of double bonds, over-oxidation and other side-reactions keeping intact the acid-sensitive functionalities. The important advantages of this procedure include (a) operational simplicity (ease of set up and work-up), (b) eliminating toxic organic solvents as reaction medium, (c) good yield of the oxidized products (68–89%) with high purity (by immobilization of the chromium by-products on the surface of alumina), (d) mild reaction conditions, (e) good selectivity and (f) general applicability accommodating a variety of substitution patterns.

4. Experimental

General: ^{1}H NMR spectra were recorded at 60 MHz on EM 360 spectrometer of Varian Associates in CCl_4 solutions and at 300 MHz and ^{13}C NMR spectra at 75-MHz on Bruker-300 spectrometer in $CDCl_3$ solutions using Me_4Si as internal standard. IR spectra were recorded on Perkin Elmer 298 spectrometer neat or in $CHCl_3$ solution. Elemental analyses were performed on Perkin Elmer C, H, N Autoanalyser. The substrates are mostly commercially available[9a] and other substrate alcohols were prepared by a standard protocol, i.e. reduction of commercially available[9a] aldehydes and ketones with $NaBH_4$[9c] or $Zn(BH_4)_2$.[17] Most of the products are also reported[9] and the references have been provided whenever necessary.

4.1. General experimental procedure for the oxidation of alcohols

The alcohol (5 mmol) was added dropwise to the PCC-Al_2O_3 [prepared by adding activated neutral alumina (4.0 g) to a solution of PCC (1.62 g, 7.5 mmol) in dry acetone followed by evaporation of solvent to get an orange-yellow easy flowing powder] in ice-cold conditions (0–5°C) with stirring and then kept at room temperature till the reaction was complete (as monitored by TLC). The product was isolated almost in pure form by filtration chromatography of the solid reaction mixture on a short plug of neutral alumina using diethyl ether as eluent followed by evaporation of the solvent under reduced pressure. It was further purified, if required, by column chromatography over silica gel or neutral alumina to yield the corresponding products as mentioned in Tables 1 and 2. For solid alcohols ethereal solution was added followed by immediate evaporation of the solvent and then the process was followed as mentioned above.

Most of the products are known compounds as substantiated by appropriate references and they were easily identified by their spectral (IR and ^1H NMR) data. The spectral data for alkyl alkanoates are presented here for ready references.

4.1.1. Heptyl heptanoate.[10a] Colourless oil, purified by column chromatography on silica gel (2% ethyl acetate-hexane) yield 71%; IR 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06 (2H, t, J=6.8 Hz, $-OCH_2$-), 2.29 (2H, t, J=7.5 Hz, $-CH_2CO-$), 1.63–1.54 (2H, m, $-CH_2-$), 1.30–1.26 (16H, m, $-CH_2-$), 0.9 (6H, t, J=6.45 Hz, $-CH_3$)].

4.1.2. Dodecyl dodecanoate.[10b] Colourless oil, purified by column chromatography on silica gel (1% ethyl acetate-hexane) yield 82%; IR 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (2H, t, J=6.5 Hz, $-OCH_2-$), 2.28 (2H, t, J=7.4 Hz, $-CH_2CO-$), 1.63–1.56 (2H, m, $-CH_2-$), 1.26–1.18 (36H, m, $-CH_2-$), 0.88 (6H, t, J=6.8 Hz, $-CH_3$).

4.1.3. 3-Methyl-1-butyl 3-methylbutanoate.[10c] Colourless oil, purified by column chromatography on silica gel (2% ethyl acetate-hexane) yield 65%; IR 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (2H, t, J=6.8 Hz, $-OCH_2-$), 2.18 (2H, d, J=6.3 Hz, $-CH_2CO-$), 1.74–1.65 (1H, m, $(CH_3)_2CH-$), 1.53–1.47 (1H, m, $(CH_3)_2CH-$), 1.19–1.12 (2H, m, CH_2-), 0.95 (6H, d, J=6.3 Hz, $(CH_3)_2CH-$), 0.92 (6H, d, J=6.6 Hz, $(CH_3)_2CH-$).

4.1.4. 2-Methyl-1-propyl 2-methylpropanoate.[10d] Colourless oil, purified by column chromatography on silica gel (pentane) yield 68%; IR 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (2H, d, J=6.6 Hz, $-OCH_2-$), 2.54 (1H, hept, J=6.0 Hz, $>CHCO-$), 1.94–1.85 (1H, m, $>CH-$), 1.52 (6H, d, J=6.0 Hz, $(CH_3)_2CH-$), 0.93 (6H, d, J=6.6 Hz, $(CH_3)_2CH-$).

4.1.5. 3-Phenyl-1-propyl 3-phenylpropanoate. Colourless oil, purified by column chromatography on silica gel (5% ethyl acetate-hexane) yield 76%; IR 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.17 (10H, m, aromatic-H), 4.08 (2H, t, J=6.5 Hz, $-OCH_2-$), 2.95 (2H, t, J=7.8 Hz, $-CH_2CO-$), 2.62 (4H, t, J=7.7 Hz, $-CH_2Ph-$), 1.94–1.90 (2H, m, $-CH_2-$). Anal. Calcd for $C_{18}H_{20}O_2$ C 80.55%, H 7.53%; Found C 80.69%, H 7.71%.

4.2. Representative oxidation of alcohols using recycled alumina

The alumina, recovered after the above-mentioned reactions was washed with 4N sulfuric acid followed by aq. sodium carbonate solution till neutral pH, dried and activated by heating at 180°C at reduced pressure (0.01 mm). A solution of benzhydrol (184 mg, 1 mmol) in minimum amount of anhydrous diethyl ether was added to PCC (323 mg, 1.5 mmol) adsorbed on aforesaid recovered and activated alumina (750 mg) and the solvent was removed instantaneously under reduced pressure at low temperature. The reaction mixture was kept at room temperature with occasional stirring for 2 hrs till the reaction was complete (monitored by TLC). The product was isolated and purified following the aforesaid method to yield benzophenone (140 mg, 77%).

4.2.1. Spectral data for 4-phenylbutan-1,4-olide. IR (neat) 1774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.18 (5H, m, aromatic-H), 5.47 (1H, dd, J_1=8.0 Hz, J_2=6.3 Hz, $-OCH-$), 2.68–2.56. (4H, m, $-CH_2-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.00 ($C{=}O$ of lactone), 139.40 (aromatic 4°$-C$), 128.88, 128.56, 125.47 (other aromatic C-Hs), 81.41 ($O-C-H$), 31.06, 29.11 ($-CH_2$-s of γ-lactone ring). Anal. Calcd for $C_{10}H_{10}O_2$, C 74.05%, H 6.21%; found C 74.29%, H 6.07%.

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