Oxidation of Alcohols with Potassium Chlorochromate

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Potassium chlorochromate, $KCrClO_3$, (KCC) is a versatile and inexpensive oxidation reagent. It converts secondary saturated, as well as allylic and benzylic alcohols to the corresponding carbonyl compounds in high yields in a variety of solvents, preferentially acetone. The reagent is highly selective. Thus, oxidation of primary alcohols gives aldehydes as the exclusive products. KCC is less useful for the transformation of primary saturated and homoallylic alcohols. Double bonds are susceptible to isomerization under the reaction conditions employed; for example, oxidation of pure nerol yields citral, and pulegol is converted to a mixture of pulegone and isopulegone. Oxidation of tertiary allylic alcohols may give the transposed aldehyde. Thus, linalool is converted to citral in high yield.

Chromium(VI) reagents are highly valuable oxidizing agents in organic chemistry.[1] In the past, chromic acid and chromium trioxide in a variety of solvents, for example acetone (Jones' reagent),[2] and chromium(VI) reagents with heterocyclic bases, for example the chromium trioxide–pyridine complex (Sarett's[3] and Collin's[4] reagents) have found widespread application for the oxidation of primary and secondary alcohols to the corresponding carbonyl compounds. More recently, pyridinium chlorochromate (PCC)[5] and pyridinium dichromate (PDC)[6] were introduced by Corey and have rapidly become the reagents most widely used for oxidation of alcohols. A variety of related heterocyclic bases also form salts with chromic acid and chlorochromic acid, many of which are selective reagents for oxidation of alcohols to carbonyl compounds. Typical reagents are 4-(N,N-dimethylamino)-pyridine chlorochromate,[7] tetrabutylammonium chlorochromate,[8] nicotine dichromate,[9] 2,2′-bipyridinium chlorochromate,[10] triethylammonium chlorochromate,[11] benzyltriethylammonium dichromate,[12] pyridinium silver dichromate,[13] pyridinium chlorochromate on polymer support[14] or on alumina,[15] and other halochromates such as pyridinium fluorochromates.[16] However, most of these

reagents suffer from some disadvantage such as instability, difficulty of preparation, requirement of a large excess of reagent, hygroscopicity, low selectivity or cost of use. In addition, many of the existing methods employing these reagents become impractical for operation on a scale larger than submolar.

This paper describes an investigation of the reactivity and scope of a new chromium(VI) oxidation agent, potassium chlorochromate, $KCrClO_3$ (KCC). The use of this compound, particularly in conjunction with 18-crown-6, for the oxidation of alcohols has previously been described by O'Brien.[17] Mitzner et al. have investigated the reaction with ethylene glycol.[18] To our knowledge, no key synthetic applications of this reagent have appeared in the literature.

KCC is a reddish–orange solid consisting of monoclinic crystals without water of hydration. It hydrolyzes readily when dissolved in water and decomposes slowly upon heating to about 150 °C. Its thermal behaviour has been investigated by Foster and Hambley.[19] However, KCC is not hygroscopic and under normal room temperature conditions is perfectly stable. Thus, no sign of decomposition was detected for a sample kept on the shelf for more than 6 years. KCC is prepared simply by dissolving potassium dichromate in ca. 6 M HCl at 70 °C and isolating the precipitated

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product after cooling. The IR spectrum (KBr) showed absorptions at 965, 950 and 916 cm^{-1}, in agreement with previously reported data.[21] Other methods of preparation involving chromyl chloride have been described in the literature.[22] KCC is very soluble in acetone (ca. 45 g/100 ml), in acetonitrile (ca. 30 g/100 ml), in ethyl acetate (ca. 14 g/100 ml), in dimethyl sulfoxide (ca. 50 g/100 ml) and in N,N-dimethylformamide, (DMF).* Solutions in acetone and acetonitrile appear to be fairly stable, particularly if stored cold. KCC is not appreciably soluble in methylene chloride, benzene or hexane.

Results and discussion

Most experiments were carried out using solutions of KCC in acetone, but acetonitrile, ethyl acetate and DMF or slurries in dichloromethane have also been used successfully. Acetone was chosen as the standard solvent for reactions, not necessarily because it may give the optimum yield, but to ensure homogeneous reaction conditions and because acetone is an inexpensive and convenient industrial solvent that gives fewer disposal problems than for example halogenated solvents. As illustrated by the results presented below, comparable or better results can often be obtained using other solvents.

A series of alcohols was oxidized by KCC. The reactions in acetone were generally accomplished merely by adding KCC as a solid or as a solution in acetone to a stirred solution of the substrate in acetone or *vice versa*. The reactions were normally exothermic. It was therefore important to ensure a controlled addition, particularly in large-scale experiments. Some representative results are shown in Table 1. Yields were determined by GLC or were those of the pure distilled or crystallized products.

Saturated primary alcohols were oxidized to the corresponding aldehydes, but only in low yields. The best results were generally obtained with acetone or dichloromethane as solvent. When monitoring the rate of formation of aldehyde, we initially observed an accumulation of

the product. After reaching a maximum, the amount of aldehyde started to decrease and eventually it disappeared. The reason for this behaviour is uncertain but may be due to polymerization, while no carboxylic acids or esters could be detected in the reaction mixtures. Although a marked increase in the yield of aldehydes is observed if anhydrous sodium bicarbonate is added to the reaction mixtures, KCC appears to be a less suitable reagent for the oxidation of saturated primary alcohols.

KCC oxidized saturated secondary alcohols to the corresponding ketones in high yields (Table 1, entries 4–11) in solvents such as acetone, dichloromethane, acetonitrile or ethyl acetate. Good yields were generally obtained from primary and secondary allylic alcohols (entries 12–17); thus, verbenol was quantitatively converted to verbenone and was isolated in 80 % yield. This reaction was also performed on a two molar scale, yielding 92 % of isolated verbenone. Isomerically pure nerol was converted to citral (74 %), illustrating that some *cis–trans* isomerization of double bonds may take place in the course of the reaction (entry 14). A similar type of reactivity has been reported for PCC.[5]

Oxidative transformations of tertiary allylic alcohols with PCC and CrO_3 have been extensively investigated.[23] We observed the same type of reactivity for KCC. Thus, reaction of linalool afforded the transposed aldehyde, citral, in 73 % yield (entry 16). Cinnamyl alcohol gave only 46 % of the expected product, cinnamaldehyde, together with 15 % of benzaldehyde (entry 17). This type of oxidative allylic cleavage reaction with di-*tert*-butylchromate has been reported by Suga et al.[24]

The oxidation of homoallylic systems gave less satisfactory results. Oxidation of 3-methyl-3-buten-1-ol gave only intractable material (entry 18), and isopulegol upon oxidation afforded only 47 % of isolated isopulegone together with ca. 10 % of pulegone (entry 19), supporting the view that KCC may facilitate double bond isomerization.

Benzylic alcohols were oxidized smoothly to the corresponding carbonyl compounds in good yields (entries 20 to 25). Benzyl alcohol was oxidized to benzaldehyde in 67 % isolated yield; the product was not oxidized further to benzoic acid upon prolonged treatment with KCC. α-Cyclopropylbenzyl alcohol (entry 25) gave the ex-

*Dissolution of KCC in DMSO and DMF is an exothermic process. 10 g could initially be dissolved in 10 ml of DMF, but upon standing a yellow precipitate was formed, identified as K_2CrO_4 by its IR spectrum: 958, 940, 910, 890, 770 cm^{-1}.

Table 1. Oxidation of selected alcohols with potassium chlorochromate.

Entry	Substrate (Solvent)[d]	Molar Ratio	Time/h	Products, yield/%[a]
1	1-Hexanol (CH_2Cl_2)	1:3	60	Hexanal, 47[b]
2	–	1:3	60	– 47[b]
3	– ($CH_2Cl_2/NaCO_3$)	1:3	60	– 72[b]
4	2-Octanol (CH_2Cl_2)	1:1	10	2-Octanone, 82[b]
5	– (CH_2Cl_2)	1:3	8	– 80[b]
6	–	1:3	10	– 66[b]
7	– (CH_3CN)	1:3	4	– 90[b]
8	– (DMF)	1:3	150	– 61[b]
9	4-*tert*-Butylcyclohexanol	1:1.5	3	4-*tert*-Butylcyclohexanone, 84
10	Menthol	1:3	3	Menthone, 85
11	Borneol	1:2	2	Camphor, 74[c]
12	Verbenol	1:2	0.5	Verbenone, 80 (99[b])
13	–	1:1	2	– 82 (92[e])
14	Nerol	1:2	2	Citral, 74
15	Pulegol	1:2	3	Pulegone + Isopulegone, 55
16	Linalool	1:2	6	Citral, 73
17	Cinnamyl alcohol	1:2	1	Cinnamaldehyde, 45; Benzaldehyde, 15
18	3-Metyl-3-buten-1-ol	1:2	2	Intractable products
19	Isopulegol	1:2	1	Isopulegone 47; Pulegone, 10
20	Benzyl alcohol	1:2	3	Benzaldehyde, 67
21	Benzyl alcohol	1:1	20	Benzaldehyde, 84[b]
22	4-Methoxybenzyl alcohol	1:2	1	4-Methoxybenzaldehyde, 67
23	4-Chlorobenzyl alcohol	1:2	1	4-Chlorobenzaldehyde, 81[c]
24	1-Phenylethanol	1:2	6	Acetophenone, 85
25	α-Cyclopropylbenzyl alcohol	1:1.5	6	Cyclopropyl phenyl ketone, 55; di(α-cyclopropylbenzyl) ether, 15
26	Benzoin	1:2	6	Benzil, 71[c]
27	Mandelic acid	1:2	5	Benzaldehyde, 89
28	Methyl mandelate	1:1.5	6	$PhCOCOOCH_3$, 82
29	PhCOCOOH	1:2	24	No reaction

[a]Unless stated otherwise, yields were of distilled or recrystallized products of at least 95 % purity by GLC. [b]Yields determined by GLC relative to an internal standard. [c]Recrystallized product. [d]Unless otherwise indicated the solvent is acetone. [e]Yield in a 2 molar scale preparative experiment.

pected ketone in 55 % yield, together with 15 % of a by-product identified as di(α-cyclopropylbenzyl) ether.

That KCC is a relatively mild oxidation agent was illustrated by the reaction with benzoin (entry 26), forming benzil in 71 % yield with no sign of bond cleavage products. On the other hand, decarboxylation took place upon oxidation of α-hydroxy acids. Thus, mandelic acid was converted to benzaldehyde in 89 % yield. In contrast to this result, methyl mandelate was transformed into methyl benzoylformate (entry 28), whereas benzoylformic acid showed no sign of reactivity (entry 29). The mechanistic aspects of the KCC-

promoted oxidation are currently being subjected to a closer investigation.

A 1:2 or 1:3 molar ratio of substrate to reagent was generally used to ensure ready and complete conversion to the product. However, a 1:1 molar ratio often gave roughly the same yield for only slightly longer reaction times. This was demonstrated for 2-octanol and benzyl alcohol in dichloromethane (entries 4 and 21) and for verbenol in acetone (entry 13).

In order to drive the reaction to completion, it was essential to use KCC in high concentrations. Thus, in GLC experiments with KCC concentrations in the range 3–5 %, complete conversion

was often difficult to achieve. With the concentration increased to 20–40%, the reactions proceeded smoothly to completion.

Conclusion. KCC is a selective, inexpensive and readily available reagent suitable for oxidation of saturated secondary alcohols, primary and secondary allylic alcohols and benzylic alcohols to the corresponding carbonyl compounds. The reactions can be carried out in a variety of solvents, for example acetone, dichloromethane or acetonitrile, with only a modest excess of the oxidant. The results obtained for the oxidation of saturated primary and homoallylic alcohols show that KCC is not a very useful reagent for the transformation of these compounds. However, KCC is potentially an attractive alternative to PCC. Being an acidic reagent, KCC also possesses some of the same limitations as PCC, such as not being applicable in the presence of acid-sensitive substrated or products. Upon aldehyde formation, little or no over-oxidation to acids can be detected. However, double bond isomerizations may take place.

Experimental

General. ^{1}H NMR spectra were recorded on a Varian EM-390 or a JEOL FX-100 NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer, and mass spectra on a AEI MS-902 spectrometer at 70 eV. GLC measurements were performed on a Varian 3700 gas chromatograph equipped with a BP-1 capillary column (25 m) or a packed column of 5% OV-17 (1.6 m).

Potassium chlorochromate, KCC was prepared from $K_2Cr_2O_7$ and HCl according to the method described by Herzog et al.[25]

Oxidation of alcohols with KCC. General procedure. To a stirred solution containing 35 mmol of the alcohol dissolved in 25 ml of acetone placed in a reaction flask equipped with a reflux condenser and an effective stirrer, was added 6.1–17.5 g (35–100 mmol) of solid KCC in small portions (the reaction is exothermic).

An alternative method is dropwise addition of 35–100 mmol of a 2 M solution of KCC in acetone to 35 mmol of the substrate in 5-10 ml of

acetone. Yet another procedure is dropwise addition of 35 mmol of the alcohol, either neat or as a solution in acetone, to 6.1–17.5 g (35–100 mmol) or KCC in 15–45 ml of acetone.

As a result of gelation and precipitation of inorganic material, it was sometimes necessary to add additional small amounts of acetone to the reaction mixture. The resulting mixture was stirred until GLC analysis revealed that all substrate was consumed. 100 ml of hexane (or methylene chloride, chloroform or benzene) was added and after stirring for an additional hour the resulting solution was filtered and concentrated under reduced pressure. In order to remove all the inorganic material the solution was filtered through a short column of silica gel or florisil. The crude product was distilled under reduced pressure or recrystallized from an appropriate solvent. The identities of the pure products were confirmed by comparison of their spectroscopic properties (IR, NMR and MS) with those of authentic samples and by GLC co-injection.

Oxidation of cinnamyl alcohol. To a solution of 5.0 g (37.3 mmol) of cinnamyl alcohol in 50 ml of acetone was added portionwise 13.0 g (74.5 mmol) of KCC. Owing to gelation it was necessary to add an additional 10 ml of acetone. The reaction mixture was stirred for 50 min and 100 ml of hexane was added. Filtration, evaporation and distillation under reduced pressure gave two products, benzaldehyde (0.58 g, 5.47 mmol, 15%) with b.p. 61–65°C at 8 mmHg, and cinnamaldehyde (2.23 g, 45%) with b.p. 108–114°C at 8 mmHg.

Oxidation of α-cyclopropylbenzyl alcohol. To a solution containing 5.0 g (33.7 mmol) of α-cyclopropylbenzyl alcohol in 5 ml of acetone was added dropwise 35 ml (70 mmol) of a 2 M solution of KCC in acetone. The reaction mixture was then stirred for 6 h. Addition of hexane, filtration and evaporation of the solvent, followed by distillation under reduced pressure, gave 2.71 g (55%) of cyclopropyl phenyl ketone, b.p. 118–120% at 11 mmHg. IR (neat): 3080, 3060, 3010, 1660, 1600, 1580, 1495, 1450, 1420, 1380, 1305, 1220, 1180, 1160, 1090, 1040, 1030, 990, 935, 870, 820, 785, 740, 700, 690 cm^{-1}. ^{1}H NMR (100 MHz, CDCl$_3$, TMS): δ 0.85–1.10 (m, 2H), 1.10–1.35 (m, 2H), 2.5–2.8 (m, 1H), 7.1–7.55 (m, 3H), 7.9–8.1 (m, 2H) ppm. MS [*m/e* (% rel.

int.)]: 146 (M$^+$)(48), 145 (9), 117 (3), 105 (100), 77 (37), 69 (8), 58 (9), 51 (10).

A by-product, 0.76 g (15 %), was distilled at 170 °C and 11 mmHg and identified as di(α-cyclopropylbenzyl) ether on the basis of its characteristic spectroscopic properties. IR (neat): 3080, 3060, 3020, 3000, 2970, 2925, 2860, 1600, 1580, 1495, 1450, 1430, 1380, 1340, 1305, 1265, 1225, 1200, 1170, 1155, 1080, 1055, 1025, 995, 970, 910, 855, 840, 770, 750, 700 cm^{-1}. ^{1}H NMR (100 MHz, CDCl$_3$, TMS): δ 0.05–0.70 (m, 8H), 0.95–1.35 (m, 2H), 3.32 (d, $J = 7.8$ Hz, 2H), 7.15–7.45 (broad singles, 10H) ppm. ^{13}C NMR (25 MHz, CDCl$_3$, TMS, proton decoupled): δ 2.65, 4.63, 18.47, 82.85, 127.01, 127.49, 128.27, 142.07 ppm. MS [m/e (% rel. int.)]: 278 (M$^+$)(0.2), 147 (16), 132 (27), 131 (100), 91 (16), 77 (4).

Oxidation of verbenol. KCC (390 g) was dissolved in 1000 ml of acetone in a flask, and a solution of 304 g (2.0 mol) of verbenol in 300 ml of acetone was added with stirring over a 1 h period. The resulting reaction mixture was stirred for 2 h and 1500 ml of hexane was added. After stirring for a further 1 h the mixture was filtered, the solvent evaporated under reduced pressure and the crude product distilled (b.p. 98–100 °C at 10 mmHg), yielding 276 g (1.84 mol, 92 %) of pure verbenone.

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