Oxidation by Cobalt(III) Acetate. Part 7.[1] Regioselective Synthesis of Substituted Cyclohexenyl Acetates

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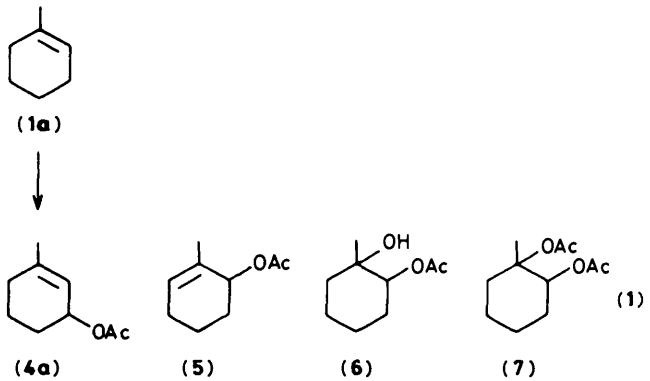
The oxidation of alkylcyclohexenes with cobalt(III) acetate has been studied in acetic acid under nitrogen. 1-Alkylcyclohexenes gave exclusively the corresponding 3-acetoxy-1-alkylcyclohexenes in good yields. Similarly, 3- and 4-methylcyclohexene afforded 3-acetoxy-6- and -5-methylcyclohexene, respectively, in surprising high selectivities. In all cases, the position α to the alkyl group was completely or largely insensitive to Co^{III}. The results can be explained in terms of steric hindrance of the alkyl group which limits the attack of Co^{III} at a hindered site.

It has recently been reported that cobalt salts are versatile reagents for oxidation of various compounds, especially for oxidation of alkylaromatic derivatives.[2-4] On the basis of kinetic results,[2,3] the reaction with cobalt(III) acetate has been considered to proceed *via* an electron-transfer mechanism including a radical cation as an incipient intermediate. However, there are few reports on the reaction of olefins in the presence of high concentration of cobalt(III) acetate. The only earlier studies on the oxidation of cyclic olefins with the oxidant, of which we are aware, are those on the reaction of cyclohexene in wet acetic acid[2] and of cycloalkenes (C_5—C_8) in AcOH–trifluoroacetic acid.[5] Our interest in the oxidation of olefins promoted us to investigate the allylic oxidation of various olefins in acetic acid under nitrogen, in which the characteristic products of cobalt(III) oxidation and their distribution were determined.[6] The present paper describes an extension of the previous study to a series of alkylcyclohexenes, since it might be expected that this procedure affords a convenient and regiospecific synthesis of substituted cyclohexenyl acetates.

1-Methylcyclohexene (**1a**) was readily oxidized with cobalt(III) acetate in acetic acid under nitrogen, yielding the allylic acetate in surprisingly high selectivity at the competing sites on the same cyclohexane ring. Thus (**1a**) gave exclusively 3-acetoxy-1-methylcyclohexene (**4a**) (59 mole %), along with only a minor amount of 6-acetoxy-1-methylcyclohexene (**5**) (1 mole %) at 313 K for 24 h; at this time, the yield of 1,2-addition products, monoacetate (**6**) and the diacetate of 1-methylcyclohexane-1,2-diol (**7**), was less than 1 mole % [equation (1)].



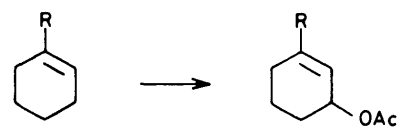
(**1a**) (**4a**) (**5**) (**6**) (**7**) (1)

It is noteworthy that the yield of the allylic acetates appreciably increased when the ratio of the initial concentration of cobalt(III) to that of 1-methylcyclohexene increased, whilst the regioselectivity of (**4a**) dramatically decreased with increased temperature. Indeed, the total yield of (**4a**) and (**5**) was 29 and 60 mole % at the ratio of $[Co^{III}]_0/[(\mathbf{1a})]_0$ = 2.5 and 5.0, respectively. At a ratio of 5.0, the allylic acetates were formed in the ratio of 59:1 at 313 K and 42:6 at 323 K, with (**4a**) predominating.

A simple explanation for the pronounced change in product distribution of the allylic acetates (**4a**) and (**5**) with temperature is that the isomerisation of (**4a**) is responsible for the formation of (**5**) at elevated temperatures. However, a facile isomerisation of (**4a**) to (**5**) should be unlikely. Indeed, an independent reaction showed that when (**4a**) was heated at 313 and 323 K for 24 h in the presence $\{[Co^{III}]_0/[(\mathbf{4a})]_0 = 2.5$ and $5.0\}$ and absence of cobalt(III) acetate, there was no formation of (**5**). The results clearly indicate that (**5**) should not result from thermal and/or cobalt-catalysed isomerisation of (**4a**). Hence the observed temperature dependence of the product distribution implies that the formation of (**5**) is a process with high activation energy compared with that of the formation of (**4a**).

In comparison with the reaction of aryl-conjugated olefins, where stoicheiometric amounts (2 equiv. per mole of olefin) or a small excess of the oxidant were found to be enough for oxidation,[1] the requirement of high oxidant concentration for the present reaction was unexpected. After heating the reaction solution at 313 K for 24 h, it was observed that cobalt(III) acetate was not completely consumed as judged from the dark green colour of the solution regardless of the presence or absence of (**1a**). In the absence of the alkene, cobalt(III) was also found to remain essentially unchanged ($[Co^{III}]/[Co^{III}]_0$ = 0.978) as determined titrimetrically. The result indicates that there is little thermal decomposition of Co^{III} and/or oxidation of AcOH by Co^{III} and therefore cobalt(III) acetate is assumed to be consumed primarily for the oxidation of the olefin. Since the unchanged olefin could be recovered only in small yield even with a low oxidant concentration, *viz.* recovered (**1a**) was 18 mole % at $[Co^{III}]_0/[(\mathbf{1a})]_0$ = 2.5, the reason for the need for high oxidant concentration is not apparent.

Oxidation of the other 1-alkylcyclohexenes (**1b**—**e**) was carried out in a manner similar to that of 1-methylcyclohexene, giving the corresponding 3-acetoxy-1-alkylcyclohexenes (**4b**—**e**) in good yields [equation (2)]. Reaction conditions (time and



(**1b-e**) (**4b-e**) (2)

b; R = Et, c; R = Pr, d; R = Pr^i, e; R = Bu^t

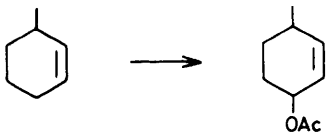
Table. Regioselective formation of the allylic acetate from Co^{III} oxidation of alkylcyclohexenes in acetic acid[a]

Cyclo-hexenes	Temp. (K)	Time (h)	[Olefin][b]	Product	Yield (mole %)
(1a)	313	24		(4a)	59
(1b)	313	24	8.5	(4b)	56
(1c)	313	24	11	(4c)	67
(1d)	313	24	4.6	(4d)	71
(1e)	333	24	2.3	(4e)	51
(2)	323	20	2.3	(8)	61
(3)	323	24	1.0	(9)	59

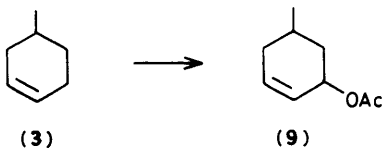
[a] Under N_2, $[Co(OAc)_3]_0$ 0.2349 mol dm^{-3}, $[Co^{III}]_0/[Olefin]_0$ 5.0 (mole ratio). [b] Recovered olefin in mole %. [c] $[Co(OAc)_3]_0$ 0.2280 mol dm^{-3}.

temperature) were determined on the basis of the reactivities of the olefins and the regioselectivities of the desired products. As with the case of 1-methylcyclohexene, the use of high concentrations of cobalt(III) acetate commonly resulted in increased yields of allylic acetates. Hence the subsequent reactions were carried out in the presence of a large excess of the oxidant. In all cases, only the tabulated products, identified by g.l.c., were formed in significant yield. Hence product analyses were confined to estimating the allylic acetates except for a few compounds involving skeletal rearrangement. Likewise no attempt was made to determine any acidic product formed.

In view of steric effect of alkyl substituents as observed above, the reactions of 3- (**2**) and 4-methylcyclohexene (**3**) were also interesting, since the former has the methyl group allylic to the double bond, and one of the allylic positions is α to the methyl group, as with 1-alkylcyclohexenes, in the latter instance. In both cases, hence, steric control of attack by Co^{III} at a hindered site should be expected. The results clearly revealed the steric effect of the methyl group; 3-methylcyclohexene gave 3-acetoxy-6-methylcyclohexene (**8**) as the main product, along with only minor amounts of 3-acetoxy-1-methylcyclohexene (2.0 mole %) and from (**3**), only 3-acetoxy-5-methylcyclohexene (**9**) was obtained.

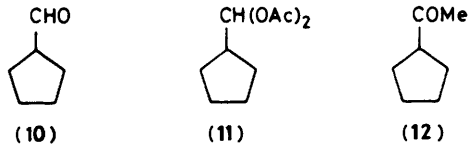


(2) (8)

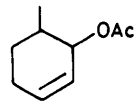


(3) (9)

In a limited comparative study, we observed that one pronounced oxidative property of cobalt(III) acetate towards some aryl-conjugated olefins is that there is no extensive formation of phenyl rearrangement products.[1] Nevertheless, with more commonly used reagents such as higher valent metal salts of lead,[7] thallium,[8,9] and mercury,[10] compounds resulting from skeletal rearrangement are formed in varying amounts, depending on the conditions employed. The products so formed from cycloalkenes and alkylcycloalkenes with the oxidants are ring-contracted aldehydes and ketones, respectively, and the reactions afford a conventional synthetic method in some cases.[10,11] To check this for the present reaction, careful g.l.c. analyses were performed, but the reaction of cyclohexene, in which 3-acetoxycyclohexene was exclusively formed,[6] gave no cyclopentanecarbaldehyde (**10**) or its diacetate (**11**). The reaction of 1-methylcyclohexene, which is expected to be more rearrangement-prone because of the additional stabilization of the ring-contracted carbocation by the methyl group, gave a similar result, *i.e.* methyl cyclopentyl ketone (**12**) was not formed.



(10) (11) (12)



(13)

In summary, oxidation of alkylcyclohexenes by cobalt(III) acetate in acetic acid affords regioselectively substituted cyclohexenyl acetates in good yields under mild conditions. The unexpected regioselectivity of the present reaction is in contrast with observations in the oxidation with 'soft' oxidants such as Pb^{IV} and Hg^{II}, *e.g.* oxidation of 1-methylcyclohexene with these oxidants gave (**5**).[12] In the case of 4-methylcyclohexene, reaction with selenium dioxide in $AcOH-Ac_2O$ afforded predominantly (**13**), along with (**8**) and (**9**).[13] Thus the present results show clearly the intervention by steric hindrance of the alkyl substituents which limit the attack of Co^{III} at a hindered site, since the position α to the alkyl group was completely or largely insensitive to Co^{III}. The allylic acetates so formed could be quite easily isolated by preparative g.l.c. or distillation without suffering from formation of a colloidal material as observed in selenium dioxide oxidation.[13]

The present reaction requires a high concentration of the oxidant and is of limited utility for large scale synthesis; however, this procedure offers two distinct advantages over alternative reagents used for allylic oxidation, *i.e.* cobalt(III) acetate is a much less expensive reagent and has lower toxicity compared with Pb^{IV}, Tl^{III}, Hg^{II}, Cr^{VI}, *etc.*

An investigation of the possible intermediates and the stereochemical considerations of the products as well as the initial interaction of Co^{III} with the alkene is beyond the scope of this report. The elucidation of these factors would provide a convincing explanation for the unexpected regioselectivity and the need for a high oxidant concentration.

Experimental

^1H N.m.r. spectra were measured for solution in $CDCl_3$ on a JEOL model JNM-FX 200 spectrometer. I.r. spectra were determined on a JASCO DS-403G spectrophotometer. G.l.c. was carried out on a Shimadzu GC-6A instrument, with a 2 m column packed with 5% PEG-20M on Chromosorb GAW DMCS. Preparative g.l.c. was performed on a Shimadzu GC-4A instrument, with a 2 m column packed with 30% PEG-20M on Celite 545, attached to a Shimadzu APP-5 fraction collector through a glass joint. Mass spectra were determined on a Shimadzu GC-MS 7000 spectrometer which was coupled *via* a heated column to the g.l.c. apparatus.

Starting Materials.—Cobalt(III) acetate was prepared by ozoniation of cobalt(II) acetate tetrahydrate in acetic acid containing acetic anhydride.[14] The conversion into Co^{III} as determined by Fe^{II} and back-titration with Ce^{IV} as well as determination of total cobalt by EDTA titration was more than 95%. 3- and 4-Methylcyclohexene were commercially available. 1-t-Butylcyclohexene was obtained by dehydration of 1-t-butylcyclohexanol with iodine.[15] Other 1-alkylcyclohexenes were prepared by conventional methods.[16] The olefins were dried over $MgSO_4$, refluxed with sodium, and distilled just before use.

Oxidation Procedures.—The following oxidation procedure is representative. 1-Methylcyclohexene (0.902 g, 0.40 mmol) was mixed with cobalt(III) acetate (5 mol equiv., 47.0 mmol in acetic acid (200 cm^3). The vessel was then flushed with dry nitrogen gas, sealed with a glass stopper, and was maintained at a controlled temperature in a thermostat without agitation. At the end of the experiment, the mixture was poured into water and the product was extracted three times with ether. A combined extract was successively washed with aqueous sodium carbonate and brine and then dried ($MgSO_4$). Evaporation of the solvent left a oil which was analysed by g.l.c. Crude products were purified by distillation or preparative g.l.c.

All the allylic acetates were identified from their g.l.c. retention times as well as mass spectroscopy. Compounds obtained from ruthenium-catalysed hydrogenation of 3-acetoxy-1- (**4a**) and -5-methylcyclohexene (**9**) were identified as a common product, 3-acetoxy-1-methylcyclohexane.

The g.l.c. yields of the allylic acetates were obtained by adding an internal standard such as biphenyl.

(**1a**): $\nu_{max.}$(neat) 3 000 (HC=), 1 725 (C=O), 1 670 (C=C), 1 435, 1 370, 1 240 (CO), 1 020 (CO), 967, 950, and 910 cm^{-1}; $\tau(CDCl_3)$ 4.5—4.58 (1 H, m, HC=), 4.71—4.85 (1 H, m, CHOAc), 7.95 (3 H, s, $OCOCH_3$), 7.83—8.45 (6 H, m, aliphatic), and 8.28 (3 H, s, CH_3); *m/e* 154 (P^+, 4.5%), 112 (15), 97 (23), 95 (26), 94 (51), 79 (100), 77 (27), and 43 (29).

(**1b**): $\nu_{max.}$(neat) 3 000 (HC=), 1 725 (C=O), 1 665 (C=C), 1 440, 1 370, 1 240 (CO), 1 020 (CO), 955, and 910 cm^{-1}; $\tau(CDCl_3)$ 4.51—4.61 (1 H, m, HC=), 4.69—4.81 (1 H, m, C*H*OAc), 7.95 (3 H, s, $OCOCH_3$), 7.90—8.51 (6 H, m, aliphatic), 7.98 (2 H, q, $-CH_2Me$), and 8.98 (3 H, t, CH_3); *m/e* 168 (P^+, 2.4%), 126 (6.2), 109 (48), 97 (24), 94 (56), 91 (28), 79 (100), 77 (37), and 43 (29).

(**1c**): $\nu_{max.}$(neat) 3 000 (HC=), 1 725 (C=O), 1 665 (C=C), 1 450, 1 370, 1 240 (CO), 1 015 (CO), 955, and 910 cm^{-1}; $\tau(CDCl_3)$ 4.52—4.60 (1 H, m, HC=), 4.69—4.82 (1 H, m, C*H*OAc), 7.94 (3 H, s, $OCOCH_3$), 7.98 (2 H, m, >CH_2–), 7.90—8.45 (6 H, m, aliphatic), 8.57 (2 H, m, CH_2), and 9.12 (3 H, t, CH_3); *m/e* 182 (P^+, 1.6%), 140 (4.0), 122 (46), 108 (27), 93 (54), 91 (35), 79 (100), 77 (37), and 43 (29).

(**1d**): $\nu_{max.}$(neat) 3 000 (HC=), 1 725 (C=O), 1 660 (C=C), 1 460, 1 370, 1 240 (CO), 1 015 (CO), 955, and 910 cm^{-1}; $\tau(CDCl_3)$ 4.53—4.62 (1 H, m, HC=), 4.68—4.80 (1 H, m, C*H*OAc), 7.70—7.91 (1 H, m, >C*H*Me_2), 7.97 (3 H, s, $OCOCH_3$), 7.93—8.48 (6 H, m, aliphatic), 8.97 (CH_3), and 9.00 (3 H, d, CH_3); *m/e* 182 (P^+, 1.5%), 139 (4.2), 122 (45), 108 (68), 104 (29), 91 (34), 79 (100), 77 (27), and 43 (36).

(**1e**): $\nu_{max.}$(neat) 3 040 (HC=), 1 725 (C=O), 1 670 (C=C), 1 460, 1 365, 1 240 (CO), 1 020 (CO), 1 015, 955, and 910 cm^{-1}; $\tau(CDCl_3)$ 4.50—4.59 (1 H, m, HC=), 4.65—4.77 (1 H, m, C*H*OAc), 7.95 (3 H, s, $OCOCH_3$), 7.83—8.50 (6 H, m, aliphatic), and 8.95 (9 H, s, Bu^t); *m/e* 196 (P^+, 1.4%), 154 (0.4), 136 (39), 121 (100), 97 (30), 93 (49), 79 (39), 77 (21), 57 (22), and 43 (29).

(**2**): $\nu_{max.}$(neat) 3 030 (HC=), 1 730 (C=O), 1 455, 1 375, 1 240 (CO), 1 020 (CO), 970, and 735 cm^{-1}; $\tau(CDCl_3)$ 4.0—4.57 (2 H, m, CH=CH), 4.68—4.97 (1 H, m, C*H*OAc), 7.95 (3 H, s, $OCOCH_3$), 7.70—9.14 (5 H, m, aliphatic and C*H*Me), and 8.97 and 9.03 (total 3 H, both d, CH_3); *m/e* 154 (P^+, 4.0%), 112 (29), 97 (25), 95 (26), 94 (65), 79 (100), 77 (17), 70 (27), 55 (14), and 43 (54).

(**3**): $\nu_{max.}$(neat) 3 035 (HC=), 1 725 (C=O), 1 455, 1 370, 1 240 (CO), 1 065, 1 020 (CO), 930, and 735 cm^{-1}; $\tau(CDCl_3)$ 3.94—4.50 (2 H, m, CH=CH), 4.57—4.89 (1 H, m, C*H*OAc), 7.95 (3 H, s, $OCOCH_3$), 7.74—9.10 (5 H, m, aliphatic and C*H*Me), and 9.0 and 9.04 (total 3 H, both d, CH_3); *m/e* 154 (P^+, 8.3%), 112 (53), 97 (22), 95 (28), 94 (33), 79 (100), 77 (20), 70 (26), and 43 (55).

Reference Compounds.—3-Acetoxy-1-alkylcyclohexenes were prepared by reduction of the corresponding 3-alkylcyclohex-2-enones[17] with $LiAlH_4$ and subsequent acetylation of the resultant alcohols with Ac_2O–pyridine (1 : 1) at ambient temperature for four days. Following the procedure described above, 3-acetoxy-6-methylcyclohexene was prepared from 4-methylcyclohex-2-enone obtained by oxidation of 3-methylcyclohexene with CrO_3–$(pyridine)_2$ complex[18] with a modification of the method of *in situ* formation of the complex in methylene dichloride.[19]

The monoacetate of 1-methylcyclohexane-1,2-diol was prepared by treating 1-methylcyclohexene (6 g, 62.5 mmol) with peracetic acid (90.2 mmol) in acetic acid containing NaOAc (2 g) at ambient temperature for five days, and after work-up the product was purified by distillation. 1-Methylcyclohexane-1,2-diol diacetate was obtained by acetylation of the corresponding monoacetate with Ac_2O–NaOAc and was purified by distillation in a glass tube oven.

Methyl cyclopentyl ketone was obtained by Friedel–Crafts acylation of cyclopentene with acetyl chloride in cyclohexane.[20] Other reference compounds (**10**) and (**11**) were prepared by oxidation of cyclohexene with $HgSO_4$ in aqueous sulphuric acid[10] and with $Tl(OAc)_3$ in acetic acid,[8] respectively.

Acknowledgements

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