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Oxidations of Alcohols with Dipyridine-chromium(VI) Oxide in Acetic Acid

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A 0.8 – 1.6 M solution of dipyridine-chromium(VI) oxide in acetic acid [1] oxidizes primary and secondary alcohols within 10 min at room temperature to the corresponding carbonyl compounds in good to excellent yields. Reaction conditions for the oxidation of some representative alcohols on a 1 – 10 g scale are given together with yields of carbonyl compounds. The reactivity of the reagent towards compounds containing other functional groups is discussed.

Dipyridine-chromium(VI) oxide,[2] suspended in pyridine (CPP), has been used for the oxidation to ketones of secondary alcohols containing acid labile protecting groups.[3,4] The reagent was satisfactory also for conversion of benzylic alcohols to aldehydes, but low yields of aldehydes were reported from aliphatic primary alcohols.[4] Other drawbacks of the method are long reaction times (10 – 24 h) and difficulties during the working up procedures.[5]

A solution of the pyridine complex has been prepared by dissolving chromium(VI) oxide (1 mol) in glacial acetic acid containing pyridine (2 mol).[1] This reagent (CPA) has been used in a rapid semimicro test for differentiation between primary and secondary alcohols.[1] The reagent has also been used on a preparative scale to oxidize 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose to the carbonyl derivative [6] which was not easily accessible at that time.

An alternative solvent for the pyridine complex is dry methylene chloride as reported by Collins *et al.*[7] They obtained high yield of aldehyde within a short reaction time even from 1-heptanol.

The facile preparation of the CPA reagent and the favourable solvent properties of acetic acid might merit its use on a preparative scale in some cases. The present paper reports suitable conditions and yields of carbonyl compounds on the oxidation of primary and secondary alcohols on a 1 – 10 g scale.

The results are presented in Table 1. The standard conditions were worked out with 1-heptanol as substrate, to ensure optimal yields of aldehydes. Under these conditions, no alcohol was detected in the reaction mixture by GLC,

Table 1. Yields of aldehydes and ketones from CPA oxidized alcohols.

Alcohol [a]	% yield	
1-Butanol	57 [c]	
2,2,2-Trimethylethanol	72 [c]	
1-Heptanol	59 [b]	
1-Heptanol (10 g)	58 [d]	
1-Decanol	66 [b]	
2-Phenylethanol	62 [b]	
Benzyl alcohol	87 [b]	
p-Hydroxybenzyl alcohol	62 [b]	
p-Methoxybenzyl alcohol	70 [d]	
o-Chlorobenzyl alcohol	88 [b]	
o-Nitrobenzyl alcohol	92 [b]	
p-Nitrobenzyl alcohol	92 [b]	
Piperonyl alcohol	86 [b]	
Cinnamyl alcohol	42 [d]	(together with 17 % benzaldehyde)
2-Octanol	68 [b]	
Cyclopentanol	66 [c]	
Cyclohexanol	75 [b]	
Methyl mandelate (10 g)	83 [e]	
Cholest-5-ene-3β-ol	85 [e]	(cholest-4-ene-3,6-dione)

[a] 0.5 g alcohol was normally used.
[b] Determined as 2,4-dinitrophenylhydrazone after ether extraction.
[c] Determined as 2,4-dinitrophenylhydrazone precipitated from the reaction mixture after SO_2 addition.
[d] Determined by GLC after ether extraction; products identified by mass spectrometry.
[e] Determined by weighing after ether extraction.

whereas heptyl heptanoate corresponding to only 2 % of the starting material was formed, evidently *via* the hemiacetal.[8]

Methyl mandelate gives a high yield of methyl phenylglyoxalate, but mandelic acid gives benzaldehyde as the main reaction product. This aldehyde is also formed from 1-phenyl-1,2-ethandiol and cinnamyl alcohol. With respect to its reactivity towards glycols and certain olefins, CPA thus resembles other Cr(VI) reagents.[9,10]

The results given in Table 1 give few aspects on the use of CPA, *e.g.* on alcohols containing acid labile groups. Examples of the stability toward CPA of representative compounds of various types are therefore given in the Experimental part.

Studies on the oxidation of cholesterol indicate that CPA is somewhat less discriminating than CPP. A high yield of cholest-4-ene-3,6-dione is obtained with CPA, whereas CP in dichloromethane [7] gives 64 % of cholest-5-ene-3-one, accompanied by isomerized oxidation products.

When the CPA reagent is reduced by an alcohol, the colour changes from red to brown-black. In most cases the reaction mixture is still homogeneous. However, occasionally a light grey precipitate appears, which contains Cr(VI) and Cr(III) compounds, pyridine, and acetic acid. The precipitate can be filtered off, following the addition of water, and the yield of carbonyl compound is not affected.

EXPERIMENTAL

Chemicals. Chromium(VI) oxide (Merck *p.a.*); acetic acid (Merck, for chromatography, 99 – 100 %); pyridine (Mallinckrodt *p.a.*). 2,4-Dinitrophenylhydrazine solution was prepared by stirring 2,4-DNPH (4 g) with 6 M HCl (600 ml) for 30 min. The solution was diluted to 1000 ml and filtered after 12 h. GLC was performed on a Varian Aerograph 1520, equipped with a flame ionisation detector.

0.8 M CPA reagent. Prepared as described by Stensiö and Wachtmeister.[1] The reagent is sensitive to light. A precipitate is formed in diffuse daylight with concomitant reduction of the Cr(VI) content (about 30 % in 40 days). The composition of this precipitate is similar to that sometimes obtained during oxidation.

1.6 M CPA reagent. Pyridine (63.2 g, 0.8 mol) was dissolved in acetic acid (150 ml) and the solution cooled to 20°. Chromium(VI) oxide (40.0 g, 0.4 mol) was added in portions with shaking. Finally, the dark red-brown solution was diluted to 250 ml volume. The reagent is convenient when large amounts of alcohol are oxidized. A mole ratio alcohol: CPA of 1:3 to 1:3.5 is then recommended.

Analysis of complex chromium precipitates. The total amount of chromium was determined by oxidizing with $HClO_4$[11] and titrating Cr(VI) with thiosulphate. The Cr(VI) content was determined by dissolving in 4 M HCl and titrating with thiosulphate.

General oxidation test. To 20 – 30 mg substance (if solid, dissolved in 0.1 ml acetic acid) 0.5 ml 0.8 M CPA is added at room temperature. If oxidation occurs, the colour of the mixture changes from dark-red to brown-black or almost black. Oxidizable alcohols give pronounced darkening within a minute. In addition, CPA rapidly oxidizes, *e.g.*, 2,5-dimethyl-2,4-hexadiene, dihydropyran, 2-chlorophenol, pyruvic acid, oxalic acid, benzilic acid, acetylacetone, 2,4-dichloroaniline, benzalaniline, 2,4-dinitrophenylhydrazine. Heptanal is oxidized moderately fast, but benzaldehyde reacts only slowly. The following compounds were not oxidized in 20 – 30 min: 1-hexene, cyclohexene, 2-methyl-2-butene, methyl phenyl ether, benzyl phenyl ether, butyl tetrahydropyranyl ether, phenyl tetrahydropyranyl ether, mesityloxide, 2-hexyl-1,3-dioxolane, 1,4-dioxaspiro[4.5]decane, 2-naphthyl acetate, ethyl 2-hexenate, ethyl acetoacetate, 1-pentylamine, cyclopentylamine, 2-phenylethylamine, 4-nitroaniline.

Standard method for oxidation of alcohols to carbonyl compounds. The alcohol (4.4 mmol) in a small flask is cooled 1 – 2 min at −5°. Solid substances are dissolved or suspended in acetic acid (2 ml). Cooled (*ca.* +15°) CPA (15 ml, 12.0 mmol) is added under stirring and cooling at −5°. After 0.5 min, the temperature of the reaction mixture is maintained at 16 ± 1° by intermittent cooling. After 10 min, the reaction is stopped by ether extraction or reduction of excess of reagent with SO_2.

Ether extraction. The oxidation mixture is diluted with water (100 ml) and extracted with ether (3 × 50 ml). The combined extracts are washed with 4 M HCl (50 ml), 1 M $NaHCO_3$ (3 × 50 ml), water (50 ml), and dried (Na_2SO_4) and evaporated. The yield of carbonyl compound is determined gravimetrically by adding 500 ml, 2,4-dinitrophenylhydrazine reagent and filtering after 24 h.

Sometimes a light grey precipitate is formed at the dilution step. If ether (50 ml) is added, and the precipitate does not dissolve, it usually consists of a complex chromium salt (*cf.* above). After filtering, the filtrate is extracted with ether as above, and the precipitate washed with ether (50 ml). The combined ether solutions are treated as above.

Determination of hydrophilic carbonyl compounds. The reaction mixture from the alcohol oxidation is cooled, and SO_2 water (*ca.* 4 g SO_2 in 50 ml water) is added slowly with cooling until the excess of Cr(VI) is just reduced, or when the colour of the solution changes from brown-black to blue or blue-violet. 500 ml 2,4-DNPH solution is added to the reduced reaction mixture.

Oxidation of 1-heptanol. A series of oxidations of 1-heptanol (500 mg, 4.3 mmol) were performed, and heptanal was determined gravimetrically after ether extraction as described above. With a mole-ratio alcohol:CPA of 1:2.7, oxidation for 10 min at different temperatures gave the following yields: 10°, 50 %; 16°, 59 %; 20°, 57 %; 25°, 54 %; without cooling 29 %. With a mole-ratio of 1:2.7, reaction at 16° at various times gave the following yields: 5 min, 63 %; 10 min, 61 %; 20 min, 42 %; 60 min, 18 %. Oxidation for 10 min at 16° and varying the mole-ratio alcohol:CPA gave: 1:0.67 (theoretical amount),; 41 %; 1:1.34, 53 %; 1:2.68, 62 %.

1-Heptanol (10.0 g, 86 mmol) was placed in a 500 ml three-necked flask, equipped with thermometer and stirrer, and cooled in an ice-salt bath. CPA (0.8 M, 290 ml, 232 mmol) cooled to 10° was added in one portion under vigorous stirring. The temperature rose to 18°, but after 1 min it could be maintained at 16°. After 10 min, the mixture was diluted with water to 1000 ml volume. A 50 ml portion was removed, diluted with water (50 ml), and extracted as above. The ether extract was concentrated to 100 ml volume, and heptanal and heptyl heptanoate were determined by GLC.

Oxidation of cholest-5-ene-3β-ol. Cholesterol (Merck) (500 mg, 1.29 mmol) was oxidized with CPA (15 ml, 12 mmol) under stirring, but without cooling. After 45 min, the clear solution was diluted with water (100 ml) and extracted with ether. Evaporation gave a product, identified as pure cholest-4-ene-4,6-dione by comparison with an authentic sample [12] (TLC, m.p., IR, UV, NMR).

Oxidation of methyl mandelate. The oxidation is slow. When the oxidation was performed at room temperature for 60 min with a mole-ratio alcohol:CPA of 1:2.7, no alcohol could be detected by NMR or with TLC (silica gel, chloroform:diethyl ether, 99:1).

Methyl mandelate (9.09 g, 54.7 mmol) was dissolved in CPA (0.8 M, 220 ml, 176 mmol). After 80 min at room temperature, the reaction mixture was diluted with water (1000 ml) and ether (400 ml), and filtered. The precipitate was washed with ether (100 ml), and the filtrate was extracted with ether (2000 ml). The combined ether solutions were washed with 4 M HCl (300 ml), 1 M $NaHCO_3$ (3 × 300 ml), and dried (Na_2SO_4). Evaporation gave crude ketoester (8.64 g, 96 %). Distillation gave 7.50 g (83 %), b.p. 132°/15 mm (lit. 137°/14 mm). The purity was confirmed by GLC-mass spectrometry.

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REFERENCES

1. Stensiö, K.-E. and Wachtmeister, C. A. *Acta Chem. Scand.* **18** (1964) 1013.
2. Sisler, H. H., Bush, J. D. and Accountius, O. E. *J. Am. Chem. Soc.* **70** (1948) 3827.
3. Poos, G. I., Arth, G. E., Beyler, R. E. and Sarett, L. H. *J. Am. Chem. Soc.* **75** (1953) 422.
4. Holum, J. R. *J. Org. Chem.* **26** (1961) 4814.
5. Snatzke, G. *Chem. Ber.* **94** (1961) 729.
6. Theander, O. *Acta Chem. Scand.* **18** (1964) 2209.
7. Collins, J. C., Hess, W. W. and Frank, F. J. *Tetrahedron Letters* **1968** 3363.
8. Cymerman Craig, J. and Horning, E. C. *J. Org. Chem.* **25** (1960) 2098.
9. Slack, R. and Waters, W. A. *J. Chem. Soc.* **1949** 594.
10. Rocek, J. and Westheimer, F. H. *J. Am. Chem. Soc.* **84** (1962) 2241.
11. Willard, H. H. and Young, P. *Ind. Eng. Chem. Anal. Ed.* **6** (1934) 48.
12. Fieser, L. F. *Org. Syn.* **IV** (1963) 189.

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