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USEFUL PROCEDURES FOR THE OXIDATION OF ALCOHOLS INVOLVING PYRIDINIUM DICHROMATE IN APROTIC MEDIA

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Despite the availability of many reagents for the oxidation of alcohols (primary, secondary, allylic, propargylic, etc.) and aldehydes, there still exists a need for new methods, especially for complex or highly sensitive substances where great selectivity and effectiveness coupled with mildness of conditions are prerequisites for success. In addition, many of the existing "mild" methods become impractical for operation on a scale greater than submolar. This note reports the results of some quite fruitful investigations of new procedures involving "non-aqueous" chromium VI reagents which were prompted by our earlier success with the (now widely used) reagent pyridinium chlorochromate[1] and the general idea that anhydrous conditions are more conducive to complexation of substrate with Cr(VI) species and therefore to mild oxidation.

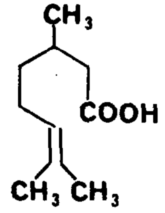
Pyridinium chlorochromate (PCC), $C_5H_5NH^+ ClCrO_3^-$, allows the efficient oxidation of a wide range of alcohols to carbonyl compounds in methylene chloride with only a modest excess of oxidant despite the fact that aqueous chlorochromate is not a very effective oxidizing species. However, the mildly acidic character[1] of PCC precludes its use with acid sensitive substrates or products, and for such unstable molecules the Collins reagent, $(C_5H_5N)_2CrO_3$,[2] which behaves as though it is neither markedly basic or acidic, is superior. Alternatively, the various oxidants derived from dimethyl sulfoxide or dimethyl sulfide[3] may be most satisfactory, depending on the specific situation. Primarily because of the inconvenience of preparing the Collins reagent and the requirement that a very large excess (typically 6-10 molar equiv) be used, our studies have been aimed at finding a nearly neutral non-aqueous Cr(VI) reagent which can serve as a more practical replacement for the Collins reagent, especially for large scale oxidations. One of the reagents which we have studied, non-aqueous pyridinium dichromate (PDC), $(C_5H_5NH^+)_2Cr_2O_7^=$, has emerged as a very useful and versatile oxidant which is clearly deserving of widespread application. Neither the reagent nor its application to the oxidation of alcohols is new. In fact, this species is probably present in the Sarett[4a] and Cornforth[4b] oxidizing mixtures. In addition, although specific reference has been made to oxidation of alcohols by PDC itself in a short note,[5] there has been no indication of any unusual effectiveness, utility or advantage to be gained by use of pre-formed PDC as a discrete oxidizing species. As far as we are aware, there have been no key synthetic applications of pre-formed PDC reagent.

Pyridinium dichromate, a stable bright orange solid, mp 144-146° C, is simply prepared in quantity (vide infra) by dissolving CrO_3 in a minimum of water, adding pyridine and collecting the precipitated product. The composition and structure of the product was confirmed by elemental analysis and the infrared spectrum (nujol mull) which showed bands at 930, 875, 765 and 730 cm^{-1} (characteristic of dichromate ion but not chromate ion).[6] PDC is very soluble in water, dimethylformamide (DMF), dimethyl sulfoxide (DMSO) or dimethylacetamide, and the solutions are relatively stable. It is sparingly soluble in methylene chloride, ethanol-free chloroform or acetone, and not noticeably soluble in hexane, toluene, ether or ethyl acetate. Although PDC dissolves in acetonitrile, the solutions are not stable. Most of our experiments have been carried out with solutions of PDC in DMF or suspensions in methylene chloride.[7]

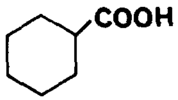
I. Some Applications of PDC in DMF

Solutions of pyridinium dichromate in DMF[8] (solubility at 25° C ca. 0.9 g/ml) rapidly oxidize allylic alcohols to α,β-unsaturated carbonyl compounds at 0° C using only 1.25 molar equiv of the PDC reagent. Thus, 2-cyclohexenol, cinnamyl alcohol and geraniol afford after a reaction time of 4-5 hr at 0° C, 2-cyclohexenone (86%), cinnamaldehyde (97%) and geranial (-10° C) (92%) (unless otherwise indicated all yields given herein refer to isolated, pure product). The reactions are very clean, and the isolation of product is simple. There is no appreciable over-oxidation in the case of the aldehydes and no $\underline{E} \rightarrow \underline{Z}$ isomerization for geraniol. In our experience this method is more convenient than and at least as efficient as other methods, e.g., activated manganese dioxide[9] or Collins[2] reagent.

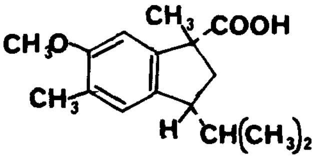
Unlike conjugated aldehydes, non-conjugated aldehydes are readily oxidized to the corresponding carboxylic acids by PDC in DMF at 25° C. Primary alcohols also afford carboxylic acids in good yields via the corresponding aldehydes which can be detected as intermediates by isolation. The acids 1-3 were obtained conveniently from the corresponding primary alcohols in the yields indicated using 3.5 equiv PDC/CH_2OH in DMF at 25° C for 7-9 hr. The acids 4 and 5 were similarly obtained (using 2 equiv PDC) from the corresponding aldehydes. This method for the direct conversion of primary alcohols to carboxylic acids is both convenient and tolerant of acid- or base-sensitive functionality. Since the oxidation of citronellol under acidic conditions is known to be complicated by cationic cyclization of the intermediate aldehyde,[1b] the formation of acid 1 by PDC-DMF instead of isopulegone provides a good indication of the mildness of the PDC-DMF reagent.



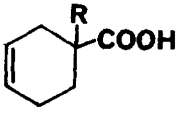
1 (83%)



2 (84%)



3 (85%)

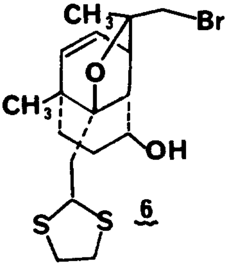


4, R = H (92%)
5, R = CH_3 (90%)

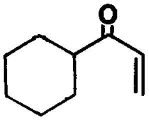
The oxidation of secondary alcohol 6 to the corresponding ketone by PDC-DMF has been found to be both the most convenient and effective method. Oxidation of 6 with 7 equiv of PDC in DMF (0.2 $\underline{M}$) at 0° C for 6 hr afforded the corresponding ketone in 95% yield. The lack of interference of the thioacetal unit in 6 is noteworthy as is the fact that the only other serviceable reagent was $(C_5H_5N)_2CrO_3$ which had to be used in large excess (10 equiv) and which afforded only 70-80% yield. It might also be noted that PDC is much more easily prepared than Collins reagent and further is more easily stored. Both PCC and Jones reagent are unsatisfactory for the oxidation of 6 since they attack the thioacetal unit.

II. Some Applications of PDC in CH_2Cl_2

Unlike PDC-DMF, the reagent PDC in CH_2Cl_2 oxidizes primary alcohols to the corresponding aldehydes and no further, regardless of the nature of the substrate. Using 1.5 molar equiv of PDC in CH_2Cl_2 at 25° C for 20-24 hr the following aldehydes were obtained cleanly from the corresponding alcohols in the indicated yields: n-decanal (98%), n-hexadecanal (94%), citronellal (92%, no isopulegone), benzaldehyde (83%, 10 hr) and p-t-butylbenzaldehyde (94%, 10 hr). Dilution of the reaction mixtures with ether, removal of the easily filterable precipitate, and concentration comprises a simple isolation of product.



6



7 (80%,9)

$C_5H_{11}C\equiv CCHO$

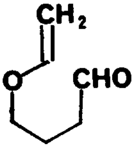
8 (70%,16)

$C_5H_{11}COC\equiv CC_5H_{11}$

9 (85%,22)

$C_5H_{11}COCH{=}CH_2$

10 (80%,9)



11 (90%,24)

The oxidation of secondary alcohols to ketones by PDC-CH_2Cl_2 is also satisfactory. Thus, 4-t-butylcyclohexanone is produced in 97% yield (100% analytical yield) by treatment of 4-t-butylcyclohexanol with 1.5 equiv of PDC in CH_2Cl_2 and 0.4 equiv of pyridinium trifluoroacetate at 25° C for 3 hr.[10] The oxidation of secondary alcohols such as 4-t-butylcyclohexanol can also be effected by PDC-DMF (94% yield).

Allylic alcohols are oxidized more rapidly by PDC-CH_2Cl_2 than their saturated analogs, and the reagent is therefore well suited to the preparation of even sensitive α,β-unsaturated carbonyl compounds. The relative rates of oxidation of 2-cyclohexenol and cyclohexanol by PDC-CH_2Cl_2 at 25° C were ca. 10:1 (by vpc analysis) with the corresponding ketones being formed in high yield. The relatively sensitive conjugated carbonyl compounds 7-11 could be prepared (% yield and reaction time in hr indicated in parentheses) using 1.5 equiv of PDC-CH_2Cl_2 at 25° C.

The oxidation of geraniol to geranial by PDC-CH_2Cl_2 (1.5 equiv) proceeds rapidly but results in some loss of double bond stereochemistry (ca. 9%). This E→Z isomerization seems to occur before oxidation to geranial (E geranial is stable under the reaction conditions), and it is possible that isomerization occurs at the stage of the intermediate chromate ester by reversible allylic rearrangement.

Preparation of PDC: Pyridine (80.6 ml) was gradually added to a cooled solution of 100 g (1 mol) of

CrO_3 in 100 ml of water at < 30° C. The solution was diluted with 400 ml of acetone and cooled to -20° C. After 3 hr the orange crystals were collected, washed with acetone and dried *in vacuo*; yield 127.2 g (68%).

General Procedural Detail: All oxidations were conducted in dry apparatus with good stirring. As little as 2 ml of DMF or 2.5 ml of CH_2Cl_2 per g of PDC may be used. Reactions involving CH_2Cl_2 solvent were diluted with ether or ether-pentane, filtered and evaporated to afford product. Last traces of Cr species can easily be removed by filtering an ethereal solution through a small amount of anhydrous magnesium sulfate or silica gel. Reactions involving DMF as solvent were worked up by pouring into 7-10 vols of water and extracting with ether or ether-pentane.[11]

References and Notes

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3. See, for example, (a) J. G. Moffatt, in "Oxidation," R. L. Augustine, ed., Vol. 2, Chap. 1, Marcel Dekker, New York, 1971; (b) K. Omura and D. Swern, *Tetrahedron*, **34**, 1651 (1978); A. K. Sharma, T. Ku, A. D. Dawson and D. Swern, *J. Org. Chem.*, **40**, 2758 (1975); and (c) E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972).
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7. Compare ref. 5.
8. The use of DMF as a solvent for some chromic acid oxidations has been reported by G. Snatzke, *Chem. Ber.*, **94**, 729 (1961).
9. For a review see, A. J. Fatiadi, *Synthesis*, 65, 133 (1976).
10. The use of a small amount of pyridinium trifluoroacetate allows the use of a minimal quantity of PDC and maintains a satisfactory reaction rate as the oxidation nears completion.
11. This work was supported by a grant from the National Science Foundation. We are indebted to Dr. M. Ishiguro, Mr. H. Pearce, and Dr. C. Shiner for the experiments on **3**, **6** and **10**.

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