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PYRIDINIUM DICHROMATE OXIDATION. MODIFICATIONS ENHANCING ITS SYNTHETIC UTILITY*.

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Summary : An improved procedure is described for extremely rapid and efficient oxidation of alcohols, by adding a small quantity of anhydrous acetic acid (AcOH) to pyridinium dichromate (PDC) and freshly activated molecular sieve powder in CH_2Cl_2 at room temperature.

Efficient oxidation of alcohols to carbonyl compounds, under mild conditions is a recurring theme in organic synthesis. In connection with our studies on 4-keto pyranosides, we had the need to synthesize uloside 1-a. Although we had obtained this ketone earlier using Collins reagent, the delicate nature of 1-a (slightly volatile under vacuum, water soluble, acid and base sensitive) required a more convenient alternative for relatively large scale preparations.

PDC[1,2] was the reagent of choice for our purpose. However like others[3,4,5], we have encountered practical difficulties such as unduly long reaction time and the requirement of a large excess of the oxidant, leading to unsatisfactory yields. During the course of our investigations, we observed a dramatic acceleration in the rate of oxidation of 1, upon adding a small quantity of anhydrous AcOH, instead of pyridinium trifluoroacetate (PTFA)[2], in refluxing CH_2Cl_2 (Table I, runs 1 and 2). But on scaling-up the reaction, we were confronted with the problem of taking it to completion without adding an excess of the oxidant.

The molecular sieve modification of PDC oxidation[3] appeared to be attractive to us. Nevertheless long reaction times or incomplete reaction were observed in the oxidation of 1, 2[4] and 3. On closer scrutiny, we identified the activation of the molecular sieve powder[6] immediately before use and the addition of anhydrous AcOH as the decisive factors for achieving reproducible and successful reactions. Accordingly, the results turned out to be excellent, as

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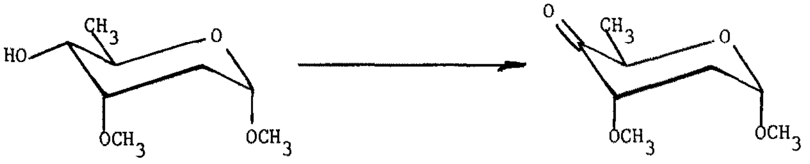
evident from the alcohols studied, simple and complex. Also, extremely fast oxidations at room temperature provide the possibility of working at lower temperatures.

Table I[a]



1 → 1-a

Run	PDC mmole	PTFA mmole	AcOH	molecular sieve[b]	Temp. °C	Time	% yield[c] (isolated)
1	1.5	0.5	-	-	40	3days	70
2	1.5	-	50µl	-	40	2h.30min	70
3	1.5	-	-	800mg	20	36h.	incompl.
4	1.5	-	100µl	800mg	20	10min	80

a) for 1mmole of 1 b) light brown powder activated immediately before use.
c) isolated yield, for pure ketone; m.p. 49-50°C $[\alpha]_D$ = 255°(C=1, $CHCl_3$)

Typical procedure : To 1 mmole of the substrate and 1.5 mmole PDC (Aldrich) in 5ml CH_2Cl_2, 800mg freshly activated molecular sieve powder[6] (3Å, Aldrich) followed by 100µl anhydrous AcOH (Prolabo) were added and stirred magnetically at room temperature. The reaction was carefully followed by t.l.c or v.p.c and worked up in the following way. The reaction mixture was stirred with celite (ca. 500mg/mmole) for about 20min., filtered and evaporated under reduced pressure with toluene to remove pyridine and/or AcOH. The resulting dark brown residue was treated with a hydrocarbon solvent or diethyl ether, filtered through anhydrous, powdered $MgSO_4$ and evaporated to give pure product[7]. For carbonyl products insoluble in these solvents, the residue was taken up in an anhydrous, aprotic solvent like ethyl acetate[8], filtered through florisil or silica gel and evaporated to obtain pure products.

The following factors were found to be useful for eliciting good results.

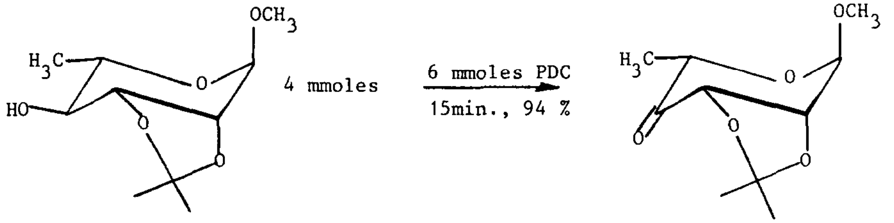
1. PDC was ground to a fine orange powder.
2. CH_2Cl_2 was redistilled over PDC and stored over activated molecular sieve beads (3Å).
3. Molecular sieve powder (3Å) was activated by heating in an enamel pan with a Bunsen burner (ca. 320°C) for 5 hours and used immediately after weighing it at room temperature. Otherwise it was stored in a hot oven (80°C) and reactivated for one half-hour before use.

4. The quantity of molecular sieve powder may be increased for hygroscopic substrates.

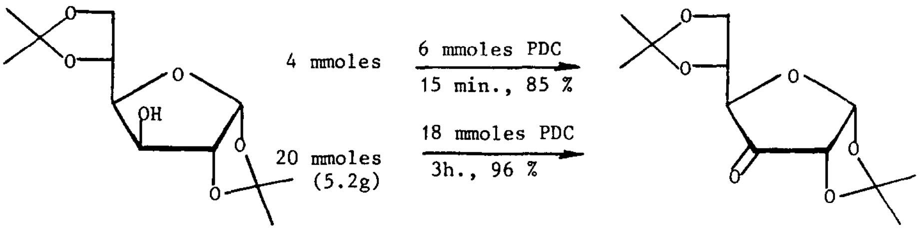
5. While a solid acid like benzoic acid can also be used, AcOH is easier to remove and also useful as a co-solvent for some substrates.

6. To avoid any exothermic reaction during large scale preparations, AcOH was added dropwise to the substrate, molecular sieve powder and PDC in CH_2Cl_2 at ca. 10°C. Stirring was thereafter continued at room temperature.

This procedure was applied to the following key intermediates of synthetic interest.



2 2-a



3 3-a

The need for fresh activation of the molecular sieve powder was illustrated by the oxidation of α-rhamnoside 2, which was complete in 5h.(without AcOH), as compared to "a period varying between 24 and 36h"[4]. This duration of 5h was dramatically reduced to 15 min. by adding AcOH, demonstrating its uniformly accelerating role. This effect assumed greater significance in the case of 1 and 3 which were incompletely oxidized even after 36h., without added acid. Efficient oxidation of sluggishly reacting 3 was achieved with only 0.9 molar equivalent of PDC.

As an extension, the 4'-OH of oleandrin (a sensitive cardiac glycoside) was oxidized to the 4'-ketone in 15 min. (70 % yield) and benzhydrol was transformed to benzophenone in 2 min. ! (91 % yield).

Table II[a]

Run	PDC mmole	PTFA mmole	AcOH	molecular sieve[b]	Temp. °C	Time	% yield (isolated)
1	1.5	0.4	-	-	20	26h.	incomplete[c]
2	1.5	-	100μl	-	20	5h.[c]	93
3	1.5	-	-	800mg	20	15min.	90
4	1.5	-	100μl	800mg	20	3min.	99[d]
5	0.7	-	100μl	800mg	20	16min.	98

a) For 1mmole of substrate b) light brown powder activated immediately before use.
c) *The minor isomer was oxidized in 8h. (run 1) and in 80 min (run 2).*
d) 15mmole reaction was successfully done with the same yield.

Table II presents the results of our investigations with 4-t-butyl cyclohexanol (isomeric mixture, Aldrich), the arch-typical example for oxidation studies. (1) It is clear that AcOH is a more efficient catalyst than PTFA[2] and the latter is not easily removed either. (2) The synergistic effect of molecular sieve-AcOH combination is strikingly shown by the reaction time of 3min. !! (3) Run 5 shows quantitative oxidation with 0.7 molar equivalent of PDC. This has implications not only on the potentiality of PDC for selective transformations and the mechanism of the oxidation process, but also on limiting the handling of toxic chromium derivatives.

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References and Notes

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6. Light brown powder (3Å,Aldrich) gives the best results; two different batches were tested (HK2724EK and KL0730JL). Oxidations were slower when molecular sieve beads (3Å) or white powder (3Å,Aldrich, AL2330CJ) were used.Beads ground to a powder can be successfully employed. The quantity of molecular sieve powder used in the oxidations was not optimised.
7. Yields are for isolated, pure products.
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