Molecular Sieve-assisted Oxidations: New Methods for Carbohydrate Derivative Oxidations

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Summary Molecular sieves catalyse pyridinium chlorochromate and pyridinium dichromate oxidation and so give rise to an efficient synthesis of ketonucleosides and ketosugars at room temperature.

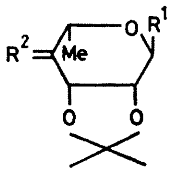
Pyridinium chlorochromate (PCC)[1] and pyridinium dichromate (PDC)[2] allow mild and large scale oxidation of a wide range of alcohols to carbonyl compounds in methylene chloride at room temperature. Unfortunately, in the case of nucleosides these conditions lead to a very long and incomplete reaction.

In order to enhance the reactivity of PCC and PDC towards nucleosides at room temperature we have tried to promote the reactions by using insoluble inorganic compounds which are active in the case of chromic[3,4] or permanganate oxidations.[5] Since attempts to catalyse the reaction by celite, alumina, and silica gel were unsuccessful we performed the oxidation using molecular sieves and found that the reaction rate was considerably accelerated (Table 1).

Table 1. Oxidation of alcohols with PCC and PDC. Influence of the molecular sieves.

Alcohol	Pyridinium derivative (mmol)	Weight[a] of molecular sieves	Reaction time[b]/min	
			A	B
Benzhydrol	PCC (2)	0·5	15	90
	PDC 1·2)	0·5	60	12 h
	PDC (1·2)[c]	0·5	30	5 h
	PDC (1·2)[d]	0·5	30	6 h
(1)	PCC (3)	0·5	60	Incomplete after 72 h
	PDC (1·5)	1	150	
	PDC (1·5)[c]	1	75	
	PDC (1·5)[d]	1	105	

[a] Expressed in g/mmol of alcohol (1 mmol) oxidized. [b] A: with molecular sieves (3 Å); B: without molecular sieves. [c] With 40 μl/mmol of $CHCl_2CO_2H$. [d] With 35 mg/mmol of pyridinium trifluoroacetate.

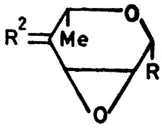


(1) R^1 = Theo; R^2 = H,OH

(2) R^1 = Theo; R^2 = O

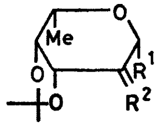
(3) R^1 = Thym; R^2 = H,OH

(4) R^1 = Thym; R^2 = O



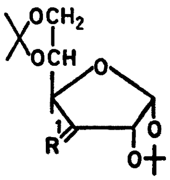
(5) R^1 = Theo; R^2 = H,OH

(6) R^1 = Theo; R^2 = O



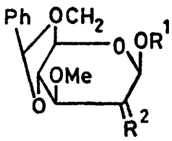
(7) R^1 = Theo; R^2 = H, OH

(8) R^1 = Theo; R^2 = O



(9) R^1 = H, OH

(10) R^1 = O



(11) R^1 = Me; R^2 = H, OH

(12) R^1 = Me; R^2 = O

(13) R^1 = Ph; R^2 = H, OH

(14) R^1 = Ph; R^2 = O

Theo = Theophyllin - 7 - yl

Thym = Thymin -1-yl

TABLE 2 Oxidation of alcohols with PCC or PDC and 3 Å molecular sieves (MS) to carbonyl compounds in dichloromethane at 25 °C

	Conditions[a]							
Alcohol	PCC[b]	PDC[b]	MS[c]	Time/min	Product	% Yield	M p /°C[f]	Ref
Benzhydrol	2	—	0·5	15	Benzophenone	100	45—47	7
,,	—	1·2	0·5	60	,,	100		
Veratryl	2	—	0·5	10	Veratraldehyde	80	42—43	8
alcohol	—	1·2	0·5	30	,,	80		
Dihydro-	2	—	0·5	15	Cholestan-3-one	90	128—129	9
cholesterol	—	1·2[d]	1	75	,,	85		
(1)	3	—	0·5	60	**(2)**	75[e]	140—141	10
,,	—	1·5[d]	1	75	,,	65[e]		
(3)	3	—	0·5	120	**(4)**	60	154—156	11
,,	—	1·5[d]	1	90	,,	50		
(5)	3	—	0·5	90	**(6)**	50	188—190	
,,	—	1·5[d]	1	90	,,	70		
(7)	4	—	1	90	**(8)**	55	205	12
(9)	4	—	1	120	**(10)**	85	105	13
(11)	3	—	1	180	**(12)**	60	172	14
(13)	4	—	1	90	**(14)**	70	165—168	14
,,	—	1·5[d]	1	60	,,	50		

[a] Amounts of PCC and PDC are expressed as mmol of Cr(VI) derivative per mmol of alcohol, amounts of 3 Å molecular sieves are expressed as g per mmol of alcohol. Dichloromethane was dried over 4 Å molecular sieves (1/8″ pellets) for 1 week. [b] Aldrich. [c] Sigma. [d] $CHCl_2CO_2H$ (40 µl/mmol of alcohol) also present. [e] The carbonyl compound was isolated after deacetalization. [f] M p.'s agreed exactly with literature values except for compound **(10)**, for which ref. 13 gives 111—112 °C.

Use of molecular sieves with PCC leads to a quick and complete oxidation of nucleosides. Furthermore we have used this new procedure with several complex alcohols and have shown that it constitutes an alternative to the Fox adaptation (refluxing benzene)[6] of the PCC oxidation of carbohydrates, particularly in the case of heat-sensitive ketosugars (Table 2).

In the case of PDC combination with molecular sieves has a wider field of application as shown by the oxidation of small molecules like benzhydrol and veratryl alcohol. As in the original procedure of Corey and Schmidt[2] the reaction can be catalysed by a weak acid like pyridinium trifluoroacetate or dichloroacetic acid which seems to be more active in the case of nucleosides.

In typical experiments the alcohols were added to a suspension of the oxidative reagent (1·5—5 equiv.) with molecular sieve powder (0·5—4 g per mmol of starting material) in dichloromethane (2·5—5 ml per mmol of alcohol). The mixture was well stirred for 10—120 min and the reaction followed by t.l.c. When the oxidation was complete the reaction mixture was diluted with diethyl ether and filtered through a glass filter filled with silica gel containing $CaSO_4$ (10%) (silicagel G, Merck Darmstadt). Removal of the solvent gave the pure carbonyl compound.

Use of benzene or dichloroethane as solvent also afforded the carbonyl compound but led to slow reactions.

Comparative studies of the molecular sieves have shown that the oxidation rate increases in the order 5 Å $<$ 10 Å $<$ 4 Å $<$ 3 Å. Furthermore with the 3 Å type the reaction can be performed with a lower weight of sieve and smaller volume of solvent.

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