

Oxidation of Alcohols to Aldehydes and Ketones

BASIC REACTIONS IN ORGANIC SYNTHESIS

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Oxidation of Alcohols to Aldehydes and Ketones:

A Guide to Current Common Practice, by Gabriel Tojo and Marcos Fernández

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A Guide to Current Common Practice

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 Springer

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This book is dedicated to the thousands of scientists cited in the references that constructed our present knowledge on the oxidation of alcohols to aldehydes and ketones. Thanks to their collective effort, the preparation of medicines, pesticides, colorants and plenty of chemicals that make life more enjoyable, is greatly facilitated.

Acknowledgements

We thank the staff of the library of the Faculty of Chemistry of the University of Santiago de Compostela (SPAIN) for their most serviceable help in collecting literature for the preparation of this book.

Preface

There is natural selection in the synthetic organic laboratory. Successful reagents find their way into specialized journals and tend to populate the researcher's benches. Sometimes, old species like active manganese dioxide in the oxidation of unsaturated alcohols are so well adapted to a certain reaction niche that they remain unchallenged for a long time. On other occasions, a successful new species like Dess Martin's periodinane enjoys a population explosion and very quickly inhabits a great number of laboratories. On the other hand, the literature is filled with promising new reagents that fell into oblivion because nobody was able to replicate the initial results on more challenging substrates.

Very few synthetic operations in Organic Chemistry match the importance of the oxidation of alcohols to aldehydes and ketones. The present book, which is a monograph on this operation, is not primarily aimed at specialized researchers interested in the development of new oxidants. Rather, it was written with the objective of being a practical guide for any kind of scientist, be it a chemist of whatever sort, a pharmacologist, a biochemist, or whoever is in the practical need to perform a certain alcohol oxidation in the most quick and reliable way. Therefore, a great emphasis is given to those oxidants that are employed most often in laboratories, because their ubiquity proves that they possess a greater reliability. Reagents appearing in only a few publications, regardless of promising potential, are only briefly mentioned. We prefer to err on the side of ignoring some good reagents, rather than including bad reagents that would lead researchers to lose their precious time.

This book is meant to be placed near working benches in laboratories, rather than on the shelves of libraries. That is why full experimental parts for important oxidations are provided. Although plenty of references from the literature are facilitated, this book was written with the aim of avoiding as much as possible the need to consult original research articles. Many researchers do not have scientific libraries possessing numerous chemical journals ready available, and, many times, although such library might be

available, it is just inconvenient to leave the laboratory in order to consult some reference.

Our aim is to facilitate a little practical help for anybody preparing new organic chemicals.

Abbreviations

Ac	acetyl	DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
acac	acetylacetonate	de	diastereomeric excess
Bn	benzyl	DIBAL-H	diisobutylaluminum hydride
Boc	<i>t</i> -butoxycarbonyl	DIPEA	diisopropylethylamine, Hünig's base
BOM	benzyloxymethyl	DMAP	4-(dimethylamino)-pyridine
b.p.	boiling point	DMB	2,5-dimethoxybenzyl
Bs	benzenesulfonyl	DME	1,2-dimethoxyethane
BSA	bis(trimethylsilyl)acetamide	DMF	<i>N,N</i> -dimethylformamide
Bu	<i>n</i> -butyl	DMP	Dess-Martin periodinane
<i>t</i> -Bu	<i>tert</i> -butyl	DMSO	dimethyl sulfoxide
Bz	benzoyl	EDC	16,14e-2,1-(3-dimethylamino propyl)-3-ethyl carbodiimide hydrochloride
ca.	circa	EE	1-ethoxyethyl
CA	Chemical Abstracts	eq.	equivalent
CAN	cerium (IV) ammonium nitrate	Et	ethyl
cat.	catalytic	Fl	9-phenylfluoren-9-yl
Cbz or Z	benzyloxycarbonyl	Fmoc	9-fluorenyl methoxycarbonyl
cHex	cyclohexyl	g	gram
CI	chemical ionization	glac.	glacial
18-Crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane	Glc	glucose
Cp	cyclopentadienyl		
CSA	camphorsulfonic acid		
d	density		
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene		
DCAA	dichloroacetic acid		
DCC	<i>N,N</i> -dicyclohexyl carbodiimide		

h	hour	PMP	<i>p</i> -methoxyphenyl
IBA	<i>o</i> -iodosobenzoic acid	POM	[(<i>p</i> -phenylphenyl)oxy]methyl
IBX	<i>o</i> -iodoxybenzoic acid	ppm	parts per million
imid.	imidazole	PPTS	pyridinium
<i>i</i> -Pr	isopropyl		<i>p</i> -toluenesulfonate
L	litre	Pr	propyl
LDA	lithium diisopropylamide	PTFA	pyridinium trifluoroacetate
m	multiplet	Py	pyridine
M	mol/L	ref.	reflux
MCPBA	<i>m</i> -chloroperoxybenzoic acid	Ref.	reference
Me	methyl	r.t.	room temperature
MEM	(2-methoxyethoxy)methyl	SEM	2-(trimethylsilyl)ethoxymethyl
min.	minute	SET	single electron transfer
MOM	methoxymethyl	TBDPS	<i>t</i> -butyldiphenylsilyl
m.p.	melting point	TBS	<i>t</i> -butyldimethylsilyl
MP	<i>p</i> -methoxyphenyl	TEMPO	2,2,6,6,-tetramethyl-1-piperidinyloxy
Ms	mesyl, methanesulfonyl		free radical
MS	molecular sieves	TEA	triethylamine
MTBE	methyl <i>t</i> -butyl ether	TES	triethylsilyl
MW	molecular weight	TFA	trifluoroacetic acid
NBS	<i>N</i> -bromosuccinimide	TFAA	trifluoroacetic anhydride
NCS	<i>N</i> -chlorosuccinimide	THF	tetrahydrofuran
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide	THP	tetrahydropyran-2-yl
NMR	nuclear magnetic resonance	T _i	internal temperature
p.	page	TIPS	triisopropylsilyl
PCC	pyridinium chlorochromate	TLC	thin layer chromatography
PDC	pyridinium dichromate	TMS	trimethylsilyl
Ph	phenyl	TMSEt	2-(trimethylsilyl)ethyl
PMB or		TPAP	tetrapropylammonium perruthenate
MPM	<i>p</i> -methoxybenzyl	Tr	triphenylmethyl, trityl
PMBOM	<i>p</i> -methoxybenzyloxymethyl	Ts	<i>p</i> -toluenesulfonyl

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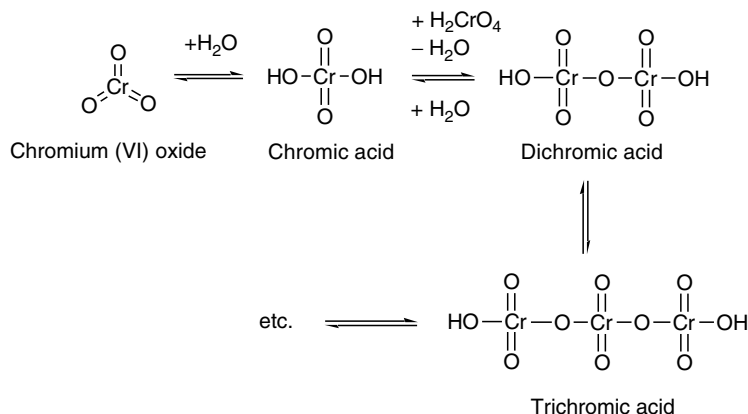
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Chromium-based Reagents

1.1. Introduction

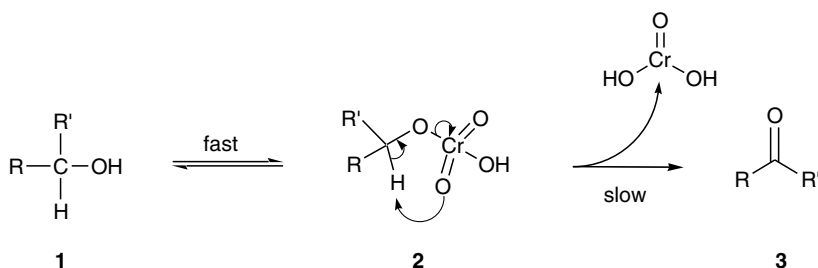
Chromium trioxide (CrO_3) is a strong oxidizing agent that appears in the form of deep-red hygroscopic crystals. Upon solution in water, it forms chromic acid that equilibrates with polymeric anhydrides.¹



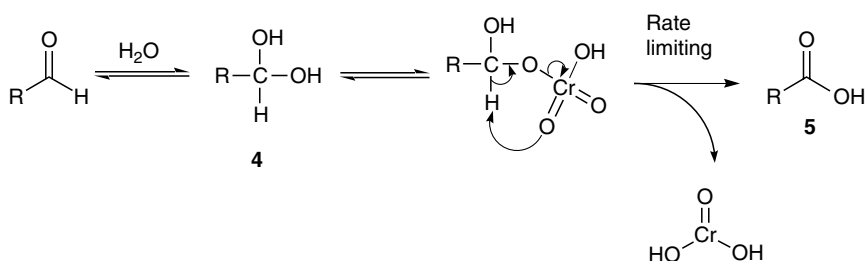
1.1.1. Jones Reagent

Although CrO_3 is soluble in some organic solvents, like *tert*-butyl alcohol, pyridine or acetic anhydride, its use in such solvents is limited, because of the tendency of the resulting solutions to explode.^{2,3} Nevertheless, acetone can safely be mixed with a solution of chromium trioxide in diluted aqueous sulfuric acid. This useful property prompted the development of the so-called *Jones oxidation*, in which a solution of chromium trioxide in diluted sulfuric acid is dropped on a solution of an organic compound in acetone. This reaction, first described by Jones,¹³ has become one of the most employed procedures for the oxidation of alcohols, and represents a seminal contribution that prompted the development of other chromium (VI) oxidants in organic synthesis.

The mechanism of the oxidation of alcohols with Jones reagent is often depicted as given below.⁴



The alcohol (1) is transformed into a chromic acid ester (2), which evolves to an aldehyde or a ketone (3). When an aldehyde is generated, it can react with water to form the hydrate (4) that can evolve as in Equation below,⁵ resulting in the formation of an acid (5).



Other chromium-based reagents are also found to oxidize alcohols, following a mechanism like the one depicted above for oxidation with chromic acid.⁴

An interesting consequence of the fast formation of the chromic ester is that, sometimes, chromium-based oxidants counter-intuitively are able to oxidize quicker alcohols possessing a greater steric hindrance, as the initially formed chromic ester releases greater tension on evolving to a carbonyl. Thus, axial alcohols are oxidized quicker than equatorial ones with chromic acid.⁶ The reverse—a somehow expected behavior—is observed, for example in oxidations with activated DMSO.⁷

Although Jones oxidation is very useful for the transformation of secondary alcohols into ketones, it can be difficult to stop the oxidation of primary alcohols at the intermediate aldehyde stage.

Useful yields of aldehydes can be obtained when the proportion of hydrate in equilibrium with the aldehyde is low (see page 12).

1.1.2. Sarett and Collins Reagents

Chromium trioxide reacts with pyridine in a highly exothermic reaction, resulting in the formation of the complex $\text{CrO}_3 \cdot 2\text{Py}$, which is soluble in organic solvents. A solution of this complex in pyridine is called *Sarett*

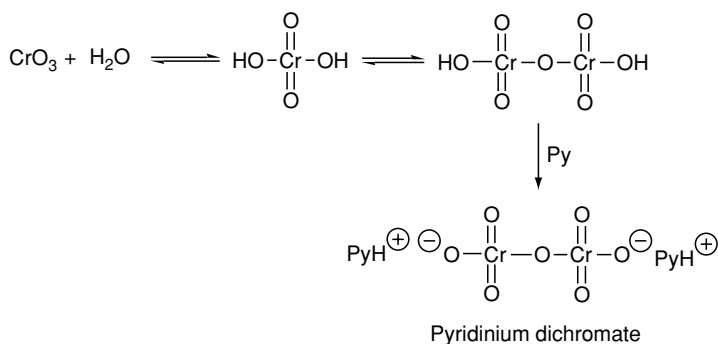
reagent.² This reagent is very efficient, not only in the oxidation of secondary alcohols to ketones, but—for its lack of water—also in the oxidation of primary alcohols to aldehydes. A useful modification of the Sarett reagent involves the use of $\text{CrO}_3 \cdot 2\text{Py}$ dissolved in methylene chloride, forming the so-called *Collins reagent*.⁸ This reagent has a number of advantages over Sarett reagent, including the use of a solvent—methylene chloride—that is not as basic as pyridine.

Both, the preparation of Sarett reagent and Collins reagent can be quite dangerous. For instance, during the generation of the $\text{CrO}_3 \cdot 2\text{Py}$ complex, chromium trioxide must be added over pyridine, as doing an inverse addition leads to an explosion.⁹ The $\text{CrO}_3 \cdot 2\text{Py}$ complex is highly hygroscopic, and can explode in the presence of organic matter. This prompted the development of the Ratcliffe variant¹⁰ of the Collins reaction, in which the $\text{CrO}_3 \cdot 2\text{Py}$ complex is formed *in situ* in methylene chloride solution, by adding chromium trioxide to a stirred solution of pyridine in methylene chloride. As this variant of the Collins reaction is much safer and convenient than both Sarett reaction and the classic Collins reaction, nowadays it is almost the only one employed in organic synthesis when $\text{CrO}_3 \cdot 2\text{Py}$ is used.

Chromium trioxide derivatives are very strong oxidizing agents that have the potential to explode in the presence of organic matter. Therefore, we suggest that no substantial changes over the standard oxidation procedures are tested during research. It is particularly dangerous to test non-standard solvents or higher temperatures than recommended. Chromium-based oxidations are mainly done in methylene chloride, which is a solvent very refractory to ignition.

1.1.3. Pyridinium Dichromate (PDC)

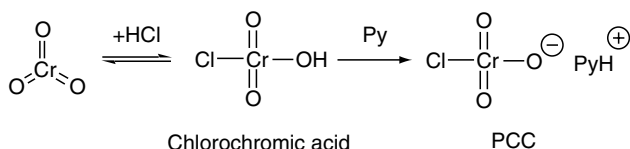
When pyridine is added to a solution of chromium trioxide in water, it is possible to obtain a precipitate of the pyridinium salt of dichromic acid, that is pyridinium dichromate (PDC).¹¹



This oxidant is a bright-orange solid that is soluble in organic solvents, and very convenient to store and manipulate, because of its lack of hydrophilicity. Pyridinium dichromate (PDC), which is normally used in dichloromethane at room temperature, is a very efficient oxidant able to transform alcohols in aldehydes and ketones in high yield. The absence of water in the reaction media prevents the over-oxidation of aldehydes into carboxylic acids.

1.1.4. Pyridinium Chlorochromate (PCC)

The interaction of CrO_3 with hydrochloric acid, in the presence of water, results in an equilibrium, in which chlorochromic acid is present. Addition of pyridine results in the formation of a precipitate of the pyridinium salt of chlorochromic acid, the so-called pyridinium chlorochromate (PCC).¹²



This reagent is a yellow-orange solid, which shares many properties with PDC. Thus, non-hygroscopic PCC is very convenient to store, and is able to transform alcohols into aldehydes and ketones in high yield when it is used in dichloromethane solution at room temperature.

1.1.5. Election of Oxidant

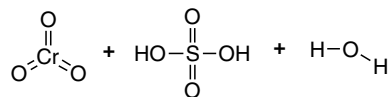
The following guidelines can help in the election of a certain chromium-based oxidant in the laboratory:

- Jones oxidation is very easy to carry out, because of the absence of need to keep anhydrous conditions. Furthermore, it is very cheap. It is the oxidation of choice for robust substrates on a big scale. It is neither suitable for very acid sensitive substrates, nor for the preparation of many aldehydes.
- Collins oxidation is very cheap, but has the added experimental difficulty of having to work under anhydrous conditions. Although sometimes it lacks the selectivity of PDC or PCC, it can produce very good yields of aldehydes and ketones in uncomplicated substrates.
- PDC and PCC are more expensive reagents that normally guarantee the best results in difficult cases.

Section 1.1. References

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1.2. Jones Oxidation



Chromium trioxide is a strong oxidizing agent, and its use in organic synthesis had to overcome two problems:

- Its lack of solubility in most organic solvents,
- Its tendency to explode in the presence of organic matter.

In 1946, Jones discovered that secondary alcohols could be efficiently oxidized to ketones by pouring a solution of chromium trioxide in diluted sulfuric acid over a solution of the alcohol in acetone.¹³ This procedure, which has proved to be quite safe, allows a sufficient contact of the alcohol with chromium oxide derivatives for a reaction to take place. Jones oxidation marked the beginning of the highly successful saga of chromium-based oxidants.

The action of sulfuric acid on chromium trioxide results in a number of equilibria, in which the major specie is chromic acid (see page 1). Thus, Jones conditions are often referred as “chromic acid” in acetone.

It is also possible to prepare a “chromic acid” solution by treating sodium dichromate ($\text{Na}_2\text{Cr}_2\text{O}_7$) or potassium dichromate ($\text{K}_2\text{Cr}_2\text{O}_7$) with sulfuric acid. Consequently, sodium¹⁴ and potassium¹⁵ dichromate can be used, instead of chromium trioxide, in Jones oxidations.

Jones oxidation is carried out under very convenient experimental conditions with no need to employ a dry environment or an inert atmosphere. It is very useful for the oxidation of secondary alcohols, while it rarely succeeds in the transformation of primary alcohols into aldehydes due to its tendency to cause over-oxidation to carboxylic acids (see page 2).

One obvious limitation of Jones oxidation is the use of acidic conditions that may cause interference with acid-sensitive functional groups. It must be mentioned that, due to the presence of separated organic and aqueous phases, containing respectively the organic substrate and sulphuric acid, such interferences are much less common than expected, and many protecting groups that can be deprotected using acid survive Jones oxidation. The concentration of sulfuric acid can be decreased in order to minimize interferences with acid-sensitive functionalities, although this causes a decrease on the oxidizing power of Jones reagent.¹⁶

1.2.1. General Procedure for Transformation of Alcohols to Ketones by Jones Oxidation

A 0.15–0.40 volume^a of concentrated sulfuric acid is added over one volume of a 1.5–4.5 M (150–450 g/L) solution of CrO_3 (MW= 100.0) in water. A fraction of the resulting red solution is dropped over a 0.01–0.5 M stirred solution of the alcohol in acetone.^b The alcohol causes the reduction of the red Cr (VI) cations to chromium species with a greenish look. A complete oxidation of the alcohol in a short time requires normally between 1.2 and 5.0 equivalents of chromium trioxide. When a TLC analysis shows that most alcohol is consumed,^{c, d} the oxidant is quenched by the addition of 0.1–0.4 volumes of 2-propanol.^e If so desired, the reaction mixture can be neutralized by the addition of saturated aqueous NaHCO_3 or diluted NaOH . The resulting mixture is extracted with an organic solvent, such as EtOAc , CH_2Cl_2 or Et_2O . The collected organic solutions are washed with brine, dried (Na_2SO_4 or MgSO_4) and concentrated, giving a crude ketone that may need some purification.

^a The use of a more limited quantity of sulfuric acid helps to avoid interferences with acid-sensitive functional groups. On the other hand, this causes a decrease in the oxidizing power of Jones reagent.¹⁶

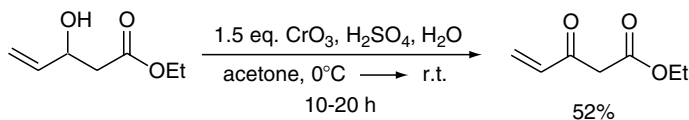
^b The solution of the alcohol in acetone can be kept either over an ice-water bath or at room temperature during all the reaction. It is also possible to keep the reaction mixture over an ice-water bath during the addition of the chromic acid solution when the major exotherm is expected, and let it reach room temperature afterwards. For reactions on a multigram scale, cooling on an ice-water bath is particularly recommended. During the oxidation of very sensitive substrates, it may be advisable to perform the entire oxidation at a temperature as low as -20°C .

^c The consumption of the alcohol can be signaled by the persistence of the red color of the chromium acid solution, which is being dropped into the reaction flask. As the red color of the solution being added is mixed with the green color of the reduced chromium species already present in the reaction flask, it may take some practice to appreciate the color changes. A sheet of white paper, placed below a reaction flask made of glass, substantially helps to distinguish these color changes.

^d It normally takes between 10 min and 12 h.

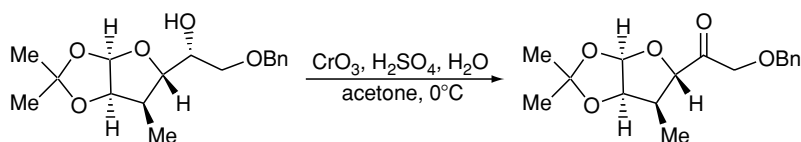
^e Other alcohols, such as MeOH , can also be used. A conspicuous change to deep green color indicates the complete quenching of the chromium (VI) species.

Some successful oxidations of secondary alcohols to ketones, using Jones reagent, are listed below:



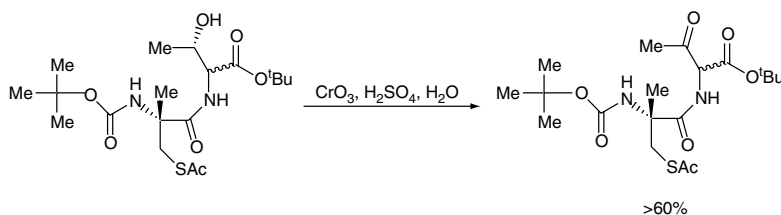
Ref. 3

A detailed description for a multigram scale preparation of an unstable ketone is provided.



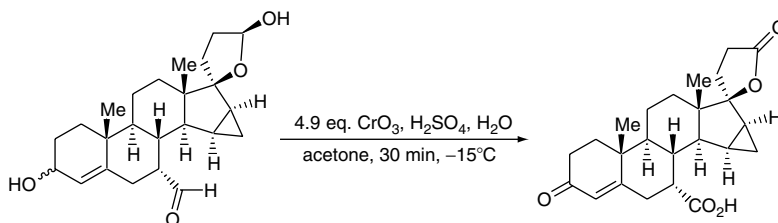
Ref. 17

The internal and the isopropylidene acetals withstand the acidic conditions.



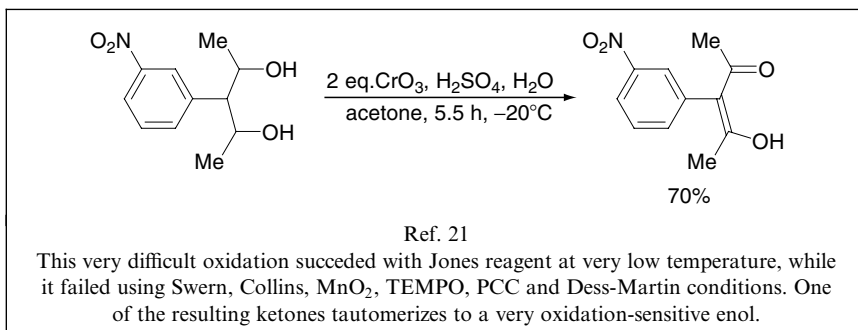
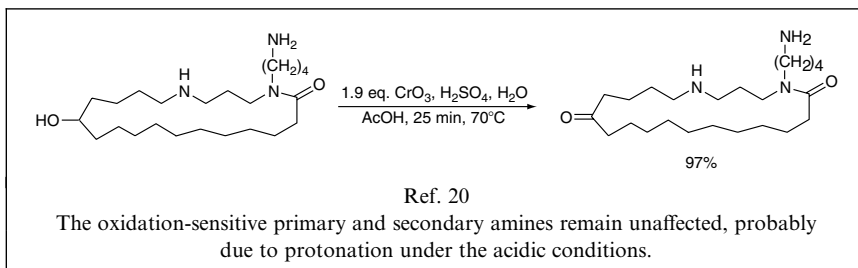
Ref. 18

Both, the very acid-sensitive *t*-butyl ester and the Boc group resist the acidic conditions.



Ref. 19

The simultaneous oxidation of an allylic alcohol, a lactol and an aldehyde is observed.



1.2.2. Protecting Group Sensitivity to Jones Oxidation

Although Jones oxidation is carried out in the presence of aqueous sulfuric acid, functionalities with a high sensitivity to acidic conditions can remain unchanged due to the segregation between the organic and aqueous phases.

Only very acid-sensitive protecting groups are hydrolyzed under the conditions of the Jones oxidation. When free alcohols result from the hydrolysis of very acid-sensitive protecting groups, they are *in situ* oxidized to ketones or carboxylic acids.

It must be mentioned that diverse acid strengths, temperatures and reaction times are used in Jones oxidation, which leads to uneven responses of the same protecting groups.

Most silyl ethers, including the ubiquitous TBS ethers,²² resist Jones oxidation, with the exception of the very acid-sensitive TMS ethers.²³

Anomalous cases are known in which the normally robust TBS ethers are hydrolyzed.²⁴ Contrastingly, rare instances have been published in which the sensitive TMS ethers remain unchanged²⁵ under Jones oxidation.

Alkoxyalkyl protected alcohols remain unchanged under Jones oxidation, except those protected with the very acid-sensitive THP group.^{26,27b}

Nevertheless, THP ethers can remain untouched in some cases,²⁷ while MOM ethers normally resist Jones oxidation²⁸, and they can be deprotected in some uncommon instances.²⁹

Table 1.1. Sensitivity of Alcohol Protecting Groups to Jones Oxidation

Protecting group		Reactivity
Silyl ethers	Remain unchanged: TMS, ^{25,35} TBS, ²² TIPS, ³⁶ TBDPS ^{37,23b}	Hydrolysis followed by oxidation to acid or ketone: TMS, ²³ TBS ²⁴
ROCH— R'	Remain unchanged: MOM, ²⁸ MEM, ³⁸ BOM, ³⁹ PMBOM, ^{36b} THP ²⁷	Hydrolysis followed by oxidation to acid or ketone: THP ^{26,27b}
Alkyl ethers	Remain unchanged: PMB, ³⁰ ^t Bu ³¹	Hydrolysis followed by oxidation to acid or ketone: Ph ₃ C-, ³² <i>p</i> -MeOPh(Ph) ₂ C- ³³
Esters	Remain unchanged	—
Alkylidene protecting diols	Remain unchanged: isopropylidene, ⁴⁰ benzylidene, ⁴¹ cyclohexylidene ⁴²	—

Benzyl, PMB³⁰ and *t*-butyl ethers are not affected,³¹ while the very acid sensitive trityl and *p*-MeOPh(Ph)₂C-ethers are hydrolyzed, and the resulting primary alcohols are oxidized to carboxylic acids.^{32,33}

In fact, it has been reported³⁴ that benzyl ethers can react with Jones reagent, resulting in the formation of ketones and benzoates. This happens under relatively harsh conditions, and normally no interference from benzyl ethers is observed during the oxidation of alcohols with Jones reagent.

Alcohols protected as esters, and diols protected as cyclic acetals resist Jones oxidation.

It is important to stress that, although MOM, TMS and THP ethers can be hydrolyzed under Jones oxidation, many cases are known in which this does not happen (Table 1.1.).

Depending on substrate and exact reaction conditions, acetals protecting both aldehydes and ketones can resist or be hydrolyzed under Jones oxidation. When the hydrolysis leads to the formation of an aldehyde, an ensuing oxidation to carboxylic acid occurs (Table 1.2.).

Regarding amine protecting groups, both amides and uretanes⁴⁹ resist the action of Jones oxidation, including the very acid-sensitive Boc protecting group.^{18,47,49}

1.2.3. Functional Group Sensitivity to Jones Oxidation

Aldehydes are oxidized to carboxylic acids by Jones oxidation; although, in certain cases, the oxidation of primary alcohols can be stopped at the aldehyde stage (see page 12).

Table 1.2. Sensitivity of Carbonyl Protecting Groups to Jones Oxidation

Protecting group		Reactivity
Aliphatic acetals	Remain unchanged: dimethyl acetal ⁴³	Hydrolysis: dimethyl acetal ⁴⁴
Cyclic acetals	Remain unchanged: ethylidene acetal ⁴⁵ 2,2-dimethylpropylidene acetal ^{45c,46}	Hydrolysis followed by oxidation to acid, or deprotection to ketone: ethylidene acetal ⁴⁷ propylidene acetal ⁴⁸

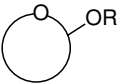
Lactols are oxidized to lactones. Depending on substrate and the precise reaction conditions, sulfides can remain unchanged⁵¹ or be transformed into sulfoxides⁵² or sulfones.⁵³ *O*-Alkyl cyclic hemiacetals including glycosides, both can remain unchanged⁵⁴ or suffer oxidation to lactones.³⁵

Most epoxides resist Jones oxidation with the exception of the very acid-labile ones,⁵⁵ that is the ones able to generate a very stable carbocation on opening.

Amines, pyridines and esters resist Jones oxidation, including the very acid-sensitive *t*-butyl esters.⁵⁶ Amines and pyridines withstand Jones oxidation, probably because they are protected by protonation under the reaction conditions.

Normally, nitrocompounds resist⁵⁷ the action of Jones reagent. Very rarely, a nitrogroup can suffer activation on contact with Jones reagent, resulting, on being attacked by a nucleophile. This reaction can compete with the normal

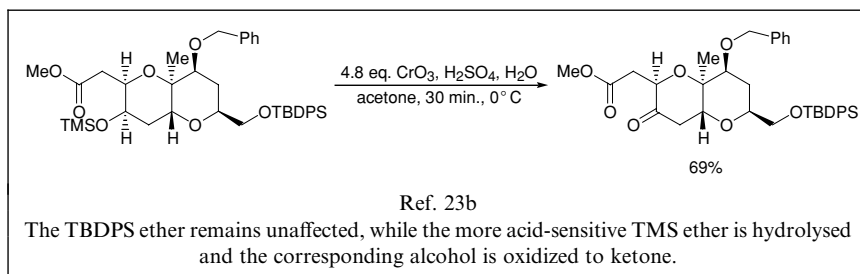
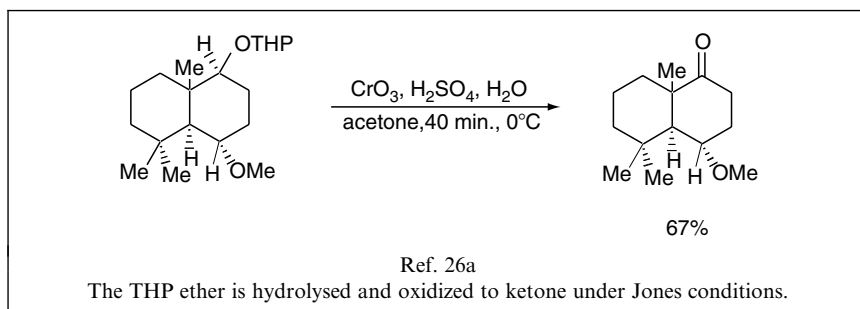
Table 1.3. Sensitivity of Functional Groups to Jones Oxidation

Functional group		Reactivity
Aldehydes	—	Oxidation to acids; ⁵⁹ nevertheless, sometimes the oxidation of primary alcohols can be stopped at the aldehyde stage ^{60,61}
Lactols	—	Oxidation to lactones ^{19,62}
Sulfides	Remain unchanged ⁵⁶	Oxidation to sulfoxides ⁵² or sulfones ⁵³
	Remain unchanged ⁵⁴	Hydrolysis followed by oxidation to acid ⁶³ or lactone ³⁵
Epoxides	Remain unchanged with the exception of the most acid-sensitive ones ⁵⁵	—
Amines and pyridines	Remain unchanged ⁶⁴	—
Esters	Remain unchanged, including the very acid sensitive <i>t</i> -butyl esters ⁵⁶	—

oxidation of the alcohol, only when the alcohol is hindered and the attack on the nitrogroup is favoured by some intramolecular process.⁵⁸

1.2.4. *In situ* Deprotection and Oxidation of Alcohols to Ketones

The sensitivity of some alcohol protecting groups to the acidic conditions of Jones oxidation allow the operation of one-pot reactions, in which deprotection of alcohols is followed by *in situ* oxidation to ketones. Some interesting synthetic applications of this principle are listed below:



The deprotection of the TBS ethers—with the corresponding oxidation to ketones or carboxylic acids—can be purposefully facilitated by the addition of some hydrofluoric acid⁶⁵ or KF⁶⁶ to the Jones reaction mixture.

