

OXIDATION

Techniques and Applications in Organic Synthesis

volume 2

edited by R. L. Augustine & D. J. Trecker

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OXIDATION

(in two volumes)

edited by

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Oxidation (IN TWO VOLUMES)

VOLUME 2

TECHNIQUES AND
APPLICATIONS IN ORGANIC SYNTHESIS

EDITOR: *Robert L. Augustine*

CATALYTIC HYDROGENATION

by Robert L. Augustine

REDUCTION

Robert L. Augustine, EDITOR

OXIDATION, VOLUME 1

Robert L. Augustine, EDITOR

OXIDATION, VOLUME 2

Robert L. Augustine and D. J. Trecker, EDITORS

Introduction to the Series

The synthetic organic chemist, must, of necessity, be well versed in the applications and subtleties of a wide variety of reactions. As time goes on and the volume of literature expands, it becomes increasingly difficult for the practicing organic chemist to be aware of all of the applications of a given reaction. It also becomes much more difficult for him to select the conditions which are most suitable for each particular application of a given reaction. It is the purpose, therefore, of this series on techniques and applications in organic synthesis to provide chemists with concise and critical evaluations of as many reactions of synthetic importance as possible.

Each volume deals with a single operation (hydrogenation, reduction, etc.), so that the information is readily available. Each chapter has been written by a chemist familiar with the various ramifications of the subject. Specific recommendations as to the most general or applicable experimental procedures are presented in bold-face type. Mechanistic considerations are included in the discussions primarily in order to enhance the understanding of the particular reactions. It was not intended for the chapters to serve as comprehensive reviews of the literature, so that only those sources which were either particularly representative or which contained unique or interesting aspects are included in the reference sections.

A number of topics which could have been included have been omitted from each volume. In many instances topics were not included either because the reaction in question was not in general use or because a recent review giving the synthetic applications of the reaction was available. In other instances, particularly concerned with reactants, coverage was omitted because a realistic evaluation of the extent of their general synthetic utilization was not available. It is planned, however, to have such reactions included in later volumes if their synthetic usefulness so warrants.

It is hoped that the series will provide the synthetic organic chemist with a valuable tool for carrying out complex syntheses, and that through its use he will have more time to devote to the attainment of his final goal.

"New parts must then be added: 'Twill follow next
If thou percuse would'st vary still its shapes,
That by like logic each arrangement still
Requires its increment of other parts."

Lucretius

Rerum Novarum

South Orange, New Jersey
August, 1967

ROBERT L. AUGUSTINE

Preface

The contents of this second volume in the series dealing with oxidation—its technique, scope, and limitations—were chosen largely on the basis of topical interest. All chapters deal with “reactions of the sixties”—oxidation genres which gained particular significance during the last decade.

- Sulfoxide-carbodiimide reactions—a selective oxidation mode presented in experimental review by one of its principal discoverers.
- Photooxygenation—an old technique which became a finely honed synthetic tool in the sixties.
- Hydroperoxide-based epoxidations—a unique process of considerable recent importance in industry.
- Metal ion-peroxide oxidations—a broad reaction class reviewed with an eye to its particular features of synthetic utility.

As in earlier volumes in the series, each chapter has been written by an experienced practitioner in the field. Literature reviews are included primarily as a means of defining the scope and useful limits of each oxidation class. Likewise, discussions concerning reaction mechanism are intended as adjuncts to explain preferred experimental conditions and to provide guidelines for the “how” of conducting the reaction.

With the subtleties of organic synthesis multiplied almost daily by the outflow of chemical literature, the synthetic chemist must increasingly turn to concise, single references on contemporary techniques. It is hoped that this volume will fill such a need.

South Orange, New Jersey
South Charleston, West Virginia
July, 1970

ROBERT L. AUGUSTINE
DAVID J. TRECKER

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Sulfoxide-Carbodiimide and Related Oxidations

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SYNTEX RESEARCH

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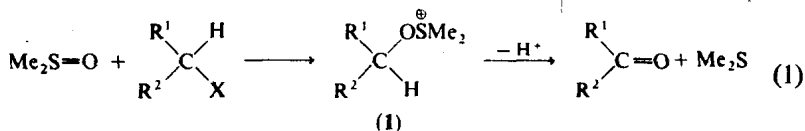
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I. INTRODUCTION

In recent years dimethyl sulfoxide (DMSO) has assumed a prominent position in organic chemistry due to its combination of unique solvent properties and specific chemical reactivities. The general properties of DMSO as both a solvent and a reactant have been the subject of several comprehensive reviews (1-4) that adequately cover the subject.

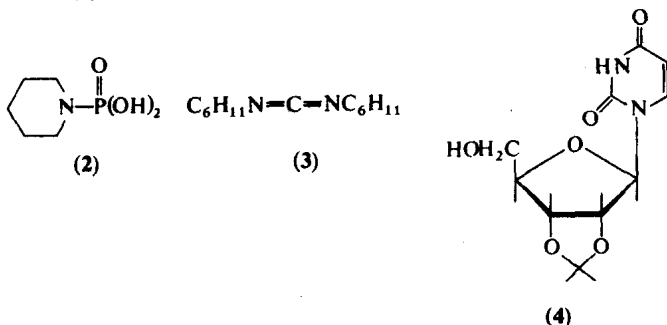
Included among the reports of DMSO reactions have been several observations of its action as an oxidizing agent (5). Thus Kornblum et al. (6) have shown that phenacyl halides react readily with DMSO at room temperature to form glyoxals or α -diketones in good yields. Less reactive halides, however, require more vigorous conditions: α -bromoesters (7) require temperatures of 70-100°, and primary (8,9) and secondary (10) alkyl iodides, or the corresponding tosylates, can be converted into aldehydes or ketones by heating at 150-170° in the presence of an acid acceptor such as sodium bicarbonate. Such oxidative reactions are limited in their synthetic value when applied to secondary α -haloketones since elimination frequently becomes a serious side reaction (11,12).

The mechanism proposed for these reactions by Hunsberger and Tien (7) involves nucleophilic displacement of the halide by DMSO with formation of an alkoxysulfonium ion (1) which subsequently loses a proton and collapses to the carbonyl compound and dimethyl sulfide as shown in Eq. (1).



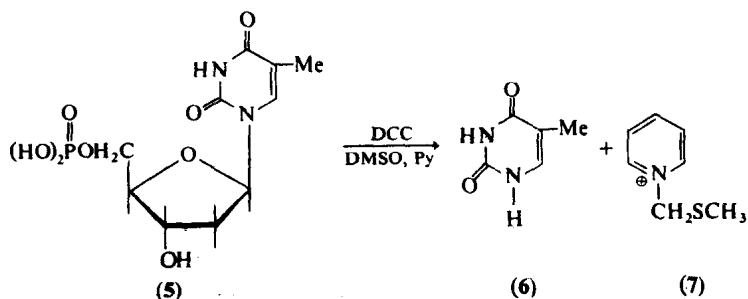
The intervention of alkoxysulfonium ions such as (1) is a common feature of many of the oxidative reactions involving DMSO. For example, they have been proposed as intermediates in the oxidative reactions of DMSO with epoxides (13,14), chloroformates (15), diazonium salts (16), and quinol acetates (17).

Several years ago, during an attempt to develop a new phosphorylating agent, we wished to investigate the reaction of *N*-phosphorylpiperidine (2) and dicyclohexylcarbodiimide (3, DCC) with 2',3'-*O*-isopropylideneuridine (4) (18). Both the *N*-phosphoryl compound and its related symmetrical pyrophosphate derivative, however, were exceedingly insoluble in pyridine, and accordingly the reaction was attempted in a mixture of pyridine and DMSO. No phosphorylation was apparent, and to rule out any adverse solvent effect, the well-known phosphorylation of (4) with 2-cyanoethyl phosphate and DCC in pyridine (19) was modified by using DMSO as a cosolvent (20). Once again, examination of the reaction by paper electrophoresis clearly showed that no phosphorylation had occurred when even 10% DMSO was added.



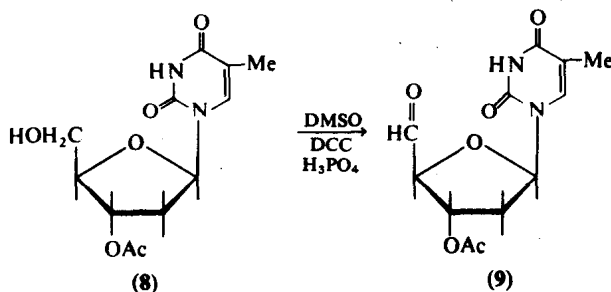
As a further test we studied the effect of added DMSO upon the well-known polymerization of thymidine 5'-phosphate (5) with DCC in

pyridine (21). In the presence of even minor amounts of DMSO the reaction took a completely anomalous course; the mixture rapidly became dark colored and emitted a foul, sulfide-like smell (20,22). Chromatographic examination after only 15 min showed that the nucleotide (5) had completely disappeared, being degraded to thymine (6) and a mixture of inorganic polyphosphates, principally ortho- and trimetaphosphates. In addition, reactions which included pyridine gave rise to varying amounts of *N*-(thiomethoxymethyl)pyridinium ion (7), which was characterized by independent synthesis.



Similar degradation of other ribo- and deoxyribonucleoside 5'-phosphates via *N*-glycosidic cleavage also was observed under similar conditions (20). Attempts to ascertain the fate of the carbohydrate moiety fail d, with reactions upon uniformly ¹⁴C-labeled nucleotides leading to a complex mixture of degradation products. To determine what structural features of the nucleotide molecule were essential for this unusual *N*-glycosidic cleavage reaction, a number of derivatives of thymidine 5'-phosphate (5) were examined. It soon became apparent that thymine release from (5) was completely suppressed if the 3'-hydroxyl function was substituted by acetyl or tetrahydropyranyl groups or if it were completely removed as in 3'-deoxythymidine 5'-phosphate. Thymidine itself was completely inert in the presence of DMSO and DCC, but upon addition of an equivalent amount of anhydrous orthophosphoric acid, an immediate reaction ensued with release of thymine. With this observation that the reaction required acidic catalysis it was then possible to examine the reactions of a number of simple, substituted nucleosides in the presence of DMSO, DCC, and anhydrous orthophosphoric acid. Such reactions showed that the release of thymine was dependent upon the presence of a free 3'-hydroxyl group, and that the presence or absence of substituents at the 5' position was unimportant.

The most significant observation in the above experiments was that, while the reaction of 3'-*O*-acetylthymidine (8) with DMSO, DCC, and anhydrous orthophosphoric acid did not lead to thymine release, the reaction product was chromatographically slightly less polar than the starting material and, unlike (8), gave a positive test for carbonyl groups when sprayed with dinitrophenylhydrazine solution. From such reactions it was possible to isolate the crystalline dinitrophenylhydrazone of 3'-*O*-acetylthymidine 5'-aldehyde (9) in 61 % yield.



Later in this chapter the oxidation of nucleosides will be considered in greater detail; for the moment it is sufficient to note that the above reaction provides an extraordinarily mild method for the oxidation of an alcohol to the corresponding carbonyl compound. In particular, the oxidation of the primary hydroxyl group of a nucleoside to the aldehyde level without the formation of any detectable carboxylic acid is unique. Other attempts at oxidizing nucleosides with platinum and oxygen (23,24), permanganate (25,26), manganese dioxide (27), and chromic oxide (28) have led to the formation of 5'-carboxylates without accumulation of detectable aldehydes. Only the closely related oxidation of 2',3'-*O*-isopropylidene-adenosine with DMSO and diphenylketen-*p*-tolimine in the presence of phosphoric acid has been reported to give the corresponding 5'-aldehyde (29). By analogy with the above it now appears clear that the glycosidic cleavage of nucleosides containing a free 3'-hydroxyl group is the consequence of a facile oxidation to the 3'-ketonucleoside followed by spontaneous β -elimination of both the heterocyclic base and the phosphate ester.

The realization that the reaction of an alcohol with DMSO, DCC, and anhydrous orthophosphoric acid leads to an efficient, yet mild, oxidation to the corresponding aldehyde or ketone has led us into a detailed study of these and related reactions. Subsequently, others have extended this type of oxidation to mechanistically closely related reactions using DMSO

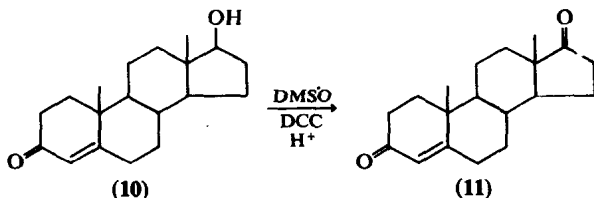
in conjunction with acetic anhydride (30), phosphorus pentoxide (31), and sulfur trioxide (32). Each of these types of reaction will be considered separately in terms of their scope and their individual advantages and limitations. An attempt has been made to cover the literature concerning these reactions as comprehensively as possible up to the spring of 1969.

Many of the combinations of reagents being discussed also can be reacted with functional groups other than alcohols leading to novel types of products (33-36). These aspects will not be considered in this chapter.

II. SULFOXIDE-CARBODIIMIDE OXIDATION OF ALCOHOLS

A. Determination of Optimal Reaction Conditions (20)

As a convenient model to quantitatively assess the effects of different reaction variables, the oxidation of testosterone (10) to androst-4-ene-3,17-dione (11) was chosen. This model offers the advantages of very facile separation of the product and reactant by thin-layer chromatography



and an intense ultraviolet chromophore for quantitative estimation. Except for the presence of trace amounts of two minor by-products (less than 1%) formed in certain cases, the only ultraviolet-absorbing products were (10) and (11), thus facilitating quantitative estimation of the rate and extent of the oxidation reaction.

The nature of the acid catalyst was first examined in a series of reactions between 1 molar equivalent of (10), 3 molar equivalents of DCC, and 0.5 molar equivalent of a variety of acids in a large excess of DMSO. The results of this study are shown in Fig. 1, from which it can be seen that a wide range of reaction rates are possible using different acids. Highly satisfactory rates of oxidation were obtained using anhydrous orthophosphoric or phosphorous acids, (11) being formed in close to 95% yield within the first 3 hr at room temperature. Subsequent experiments actually showed that oxidation was essentially complete within

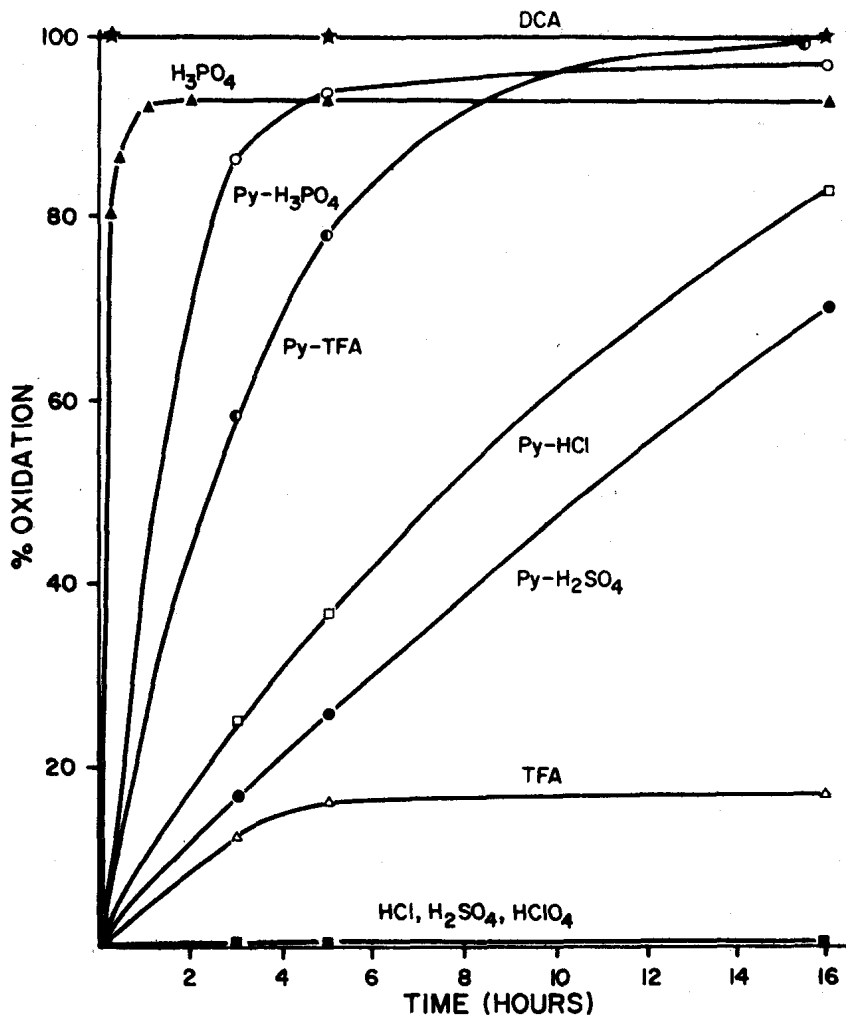


Fig. 1. Rates of oxidation of testosterone using different acids. Each reaction contained testosterone (0.1 mmole), DCC (0.3 mmole), and the appropriate acid (0.05 mmole) in DMSO (0.5 ml). The extent of reaction was measured by quantitative thin-layer chromatography of evaporated aliquots.

45 min when these acids were used. On the other hand, no oxidation was observed when mineral acids were used, and only a slow, partial reaction took place with strong organic acids such as trifluoroacetic acid. All of these strong acids, however, became satisfactory proton sources when

used as their pyridinium salts. Oxidations using the pyridinium salts of mineral acids tended to be rather slow and often incomplete, but the pyridinium salts of orthophosphoric and trifluoroacetic acids led to extremely clean reactions. For example, when pyridinium trifluoroacetate was used, a single ultraviolet-absorbing material was present following oxidation of (10). Trialkylammonium salts of strong acids, however, failed to provide adequate oxidation. Comparisons of the efficiencies of several other groups of acids led to some further interesting correlations. Thus, although oxidation of (10) to (11) reached a constant value of 92% in about 45 min using anhydrous orthophosphoric acid, the reaction was decidedly faster using monophenyl phosphate and reached a plateau at 90% oxidation within 15 min. On the other hand, diphenyl phosphate functioned very poorly and led to only 3% of (11) after 3 hr and to 37% after 5 days. A similar comparison showed that acetic acid (pK 4.76) and trichloroacetic acid (pK 0.66) did not support the oxidation of (10); that monochloroacetic acid (pK 2.86) led to slow and incomplete reaction; and that dichloroacetic acid (pK 1.25) gave complete oxidation with less than 1% impurities within 6 min. Our experience has been that dichloroacetic acid provides the most rapid oxidations of any acid we have tested. Indeed, it has been suggested (37) that in certain cases (e.g., the oxidation of *estra*-1,3,5(10)-triene-3,11 α ,17 β -triol-3-methyl ether to the corresponding 11,17-dione) this acid is essential to obtain a high yield of product.

From the above it is clear that acids of intermediate strength are necessary to obtain satisfactory oxidation. Both very weak acids (e.g., acetic acid) and very strong acids (e.g., mineral acids) fail since, as will be discussed later, the reaction mechanism involves both acid- and base-catalyzed steps, and a suitable balance between the two must be reached. **Our general experience is that free orthophosphoric acid, dichloroacetic acid, and pyridinium trifluoroacetate are the most satisfactory acids for preparative purposes.** Frequently, the use of phosphoric acid leads to the formation of minor amounts (up to perhaps 5%) of by-products, usually the thiomethoxymethyl ether of the starting alcohol (e.g., (12) from oxidation of testosterone), whereas this side reaction is considerably reduced with pyridinium trifluoroacetate or dichloroacetic acid. On the other hand, the use of the latter two acids gives rise to a side reaction with DCC giving *N*-acylureas. Reactions using pyridinium trifluoroacetate, for example, give appreciable amounts of *N*-trifluoroacetyl *N,N'*-dicyclohexylurea (13), a very faintly ultraviolet-absorbing compound that is rather difficult to detect with many spray reagents used on thin-layer silica plates. Since acylureas such as (13) are very soluble in most organic solvents,