Reagents for Organic Synthesis

VOLUME 2

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WILEY-INTERSCIENCE

A DIVISION OF JOHN WILEY & SONS
NEW YORK · LONDON · SYDNEY · TORONTO

10 9 8 7 6 5 4 3 2

Library of Congress Catalogue Card Number: 66-27894

SBN 471 25876 8

Printed in the United States of America

PREFACE

Favorable comments expressed both in formal reviews and personally have encouraged us to present this second volume of *Reagents*, the size of which measures the amount of new material that has accumulated in the two and a half years since the closing date of August 23, 1966, for Volume 1. This second volume contains 1320 additional references to 390 reagents discussed in the first volume and 550 references to 226 reagents reviewed by us now for the first time. Most of the latter were introduced since the first volume was written, but a few are old reagents recently reintroduced into modern research. It is interesting that in this period more new oxidizing agents (17) and reducing agents (11) were discovered. However, it appears that the biggest field for new reagents is that of the organometallic compounds. Thus we have discussed in this volume 34 new organometallic reagents, compared with a total of only 50 in the larger first volume. New organophosphorous and organosulfur compounds are also proving increasingly useful.

We are indebted to Research Corporation for a grant in support of the project and to colleagues for help in the preparation of this volume. Many have sent us useful information or have checked sections pertaining to their own work. Some have sent us contributions for which we are most grateful.

The formulas were drawn by Miss Theodora S. Lytle, who also typed the manuscript.

Cambridge, Massachusetts
February 18, 1969

MARY FIESER
LOUIS F. FIESER

CONTENTS

Introduction

Arrangement. Suppliers mentioned in the text are listed in a section placed before the indexes and easily located by an indenture.

For enhanced usefulness the book is provided not only with a subject and an author index but also with an index of types, that is, types of reactions or types of compounds, for example: acetylation, bromination, characterization (of a, b, c, etc.), decarboxylation, or: π-acids, benzyne precursors, carbene precursors, diimide precursors. Listed alphabetically under each such entry are all the reagents which figure in the operation or group cited, whether as prime reactant, catalyst, solvent, scavenger, etc. A given reagent may fit appropriately in two or more categories. When a reagent does not fit easily into a reasonable category, we leave it unclassified rather than make a forced assignment. With no less than 109 reagents available as oxidants and 115 for use as reducing reagents, it seemed out of the question to attempt to indicate in the index of types further details about these general reactions. In a few instances a procedure cited for the preparation of one reagent provides a good example of the use of another one. For example, a preferred route to allene is by reaction of 2,3-dichloropropene with zinc dust and ethanol; in the index of types the entries under "dechlorination" include "Zinc dust–ethanol, *see* Allene, preparation."

Names and spelling. One guideline we have followed is the rule recently adopted by *Organic Syntheses* that when an ester, ether, or peroxide contains two or more alkyl, aryl, or acyl groups the name must indicate the number of such groups:

Formula	*Correct*	*Incorrect*
$(CH_3)_2O$	Dimethyl ether	Methyl ether
$(C_2H_5O)_2SO_2$	Diethyl sulfate	Ethyl sulfate
$(C_6H_5)_2O$	Diphenyl ether	Phenyl ether
$(CO_2CH_3)_2$	Dimethyl oxalate	Methyl oxalate
$CH_2(CO_2C_2H_5)_2$	Diethyl malonate	Ethyl malonate
$(C_6H_5COO)_2$	Dibenzoyl peroxide	Benzoyl peroxide
$HC(OC_2H_5)_3$	Triethyl orthoformate	Ethyl orthoformate
$(C_2H_5O)_4C$	Tetraethyl orthocarbonate	Ethyl orthocarbonate

That the situation previously was highly confused is evident from the following entries in the index of *Org. Syn., Coll. Vol.*, 4: "Diethyl oxalate" and "Diethyl malonate" (both correct), but "Ethyl orthoformate" and "Ethyl orthocarbonate" (both incorrect). The following entry is describable as a double error: "Triethyl orthoformate, *see* Ethyl orthoformate." To locate all references to a given ester, it is thus necessary to search under two names. We urge suppliers to revise their catalogs in accordance with the rule cited. In this book we do not even list, with cross references, names which we consider to be incorrect.

Similar reform in the nomenclature of polyhalogen compounds may come some day, but for the present we consider it imprudent to do more than make a start.

Thus the correct names for BF_3 and for $ClCH_2CH_2Cl$ surely are boron trifluoride and ethylene dichloride, and we feel no restraint from using them. However, although the names methylene chloride for CH_2Cl_2 and aluminum chloride for $AlCl_3$ seem incorrect, we cannot bring ourselves to break with tradition and employ other names.

As explained in our *Style Guide for Chemists* (p. 77), we disapprove of the weak-sounding dioxăn, furăn, tryptophăn, and urethăn and add the letter *e* to these words to produce the strong pronunciations dioxāne, furāne, tryptophāne, and urethāne. For the same reason we favor desoxo- and desoxy- over deoxo- and deoxy-.

Abbreviations. Short forms of abbreviations of journal titles are as follows:

Journal of the American Chemical Society
Angewandte Chemie
Angewandte Chemie, international Edition in English
Annalen der Chemie
Annales de chimie (Paris)
Australian Journal of Chemistry
Chemische Berichte (formerly Berichte der deutschen chemischen Gesellschaft)
Bulletin de la société chimique de France
Canadian Journal of Chemistry
Chemical Communications
Chemical and Pharmaceutical Bulletin
Acta Chemica Scandinavica
Collection of Czechoslovak Chemical Communications
Comptes rendus hebdomadaires des séances de l'académie des sciences
Gazzetta chimica italiana
Helvetica Chimica Acta
Journal of the Chemical Society (London)
Journal of Heterocyclic Chemistry
Journal of Organic Chemistry
Journal of Organometallic Chemistry
Monatshefte für Chemie
Organic Syntheses
Organic Syntheses, Collective Volume
Recueil des travaux chimique des Pays-Bas (The Netherlands)

The book by one of us, *Organic Experiments*, 2nd Ed., D. C. Heath and Co., Boston (1968), is referred to as *Org. Expts.*

Abbreviations

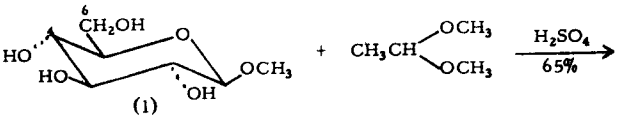
Ac	Acetyl
AcOH	Acetic acid
BuOH	Butanol
Bz	Benzoyl
Cathyl	Carboethoxy
Cb	Carbobenzoxy
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

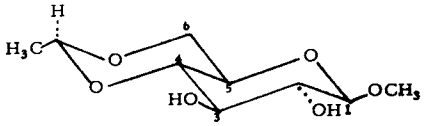
Diglyme	Diethylene glycol dimethyl ether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNF	2,4-Dinitrofluoro-benzene
DNP	2,4-Dinitrophenyl-hydrazone
EtOH	Ethanol
Glyme	1,2-Dimethoxyethane
HMPT	Hexamethylpolyphosphoric triamide
MeOH	Methanol
Ms	Mesyl, CH_3SO_2
NBS	N-Bromosuccinimide
Ph	Phenyl
Phth	Phthaloyl
PPA	Polyphosphoric acid
Py	Pyridine
THF	Tetrahydrofurane
Triglyme	Triethylene glycol dimethyl ether
Trityl	$(C_6H_5)_3C-$
Ts	Tosyl, p-$CH_3C_6H_4SO_2-$
TsCl	Tosyl chloride
TsOH	Tosic acid, p-$CH_3C_6H_4SO_3H$

A

Acetaldehyde dimethylacetal (1,1-Dimethoxyethane), $CH_3CH(OCH_3)_2$ [**1**, 3, before **Acetaldoxime**]. Mol. wt. 90.12, b.p. 63–65°. Suppliers: B, C, E, F. Fl. (Fluka), K.-L. (Koch-Light), Sch. (Schuchardt).

O'Meara and Shepherd[1] found the reagent useful for the conversion of aldopyranoses into ethylidene derivatives. Thus 2.5 ml. of concd. sulfuric acid was added dropwise to a stirred suspension of 58 g. of methyl β-D-glucopyranoside (1) in 250 ml. of acetaldehyde dimethylacetal. The mixture was shaken for 48 hrs., filtered, and the solid product (2) collected and crystallized twice from ethanol. Methyl 4:6-





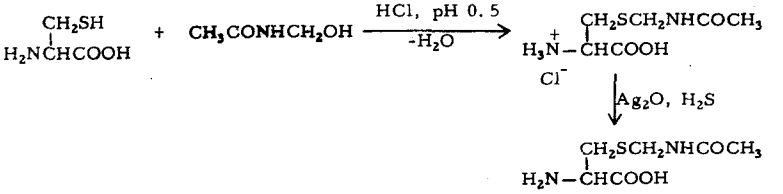
O-ethylidene-β-D-glucopyranoside (2) was obtained thus in a high state of purity in 65% yield. This transformation previously had been accomplished by treating paraldehyde with the glucoside in the presence of sulfuric acid,[2] but the yields were variable owing to a side reaction which gives methyl 4:6-O-ethylidene-2:3-O-oxidodiethylidene-β-D-glucopyranoside. A second British group[3] has confirmed the observation that the side reaction can be eliminated by use of acetaldehyde dimethylacetal.

[1]D. O'Meara and D. M. Shepherd, *J. Chem. Soc.*, 4232 (1955)
[2]B. Helferich and H. Appel, *Ber.*, **64**, 1841 (1931); J. Dewar and G. Fort, *J. Chem. Soc.*, 492 (1944)
[3]J. Honeyman and T. C. Stening, *ibid.*, 3316 (1957)

Acetamidomethanol, $CH_3CONHCH_2OH$ [**1**, 3, before **Acetic anhydride**]. Mol. wt. 89.10, m.p. 50–52°.

Preparation from acetamide and formaldehyde.[1]

Protection of cysteine.[2] The reagent reacts with L-cysteine in hydrochloric acid at pH 0.5 at 25° to give S-acetamidomethyl-L-cysteine hydrochloride from which the free base can be obtained by treatment with Ag_2O and then H_2S. The S-acetamidomethyl group is stable to acidic reagents commonly used for removal of acid-labile substituents: CF_3COOH, HBr, HCl, HF; but it is removed in high yield by 2 equiv. of Hg(II) salts at pH 4 at room temperature, conditions that do not affect such groups as carbobenzoxy, N-*t*-butyloxycarbonyl, and S-benzyl. The solubility



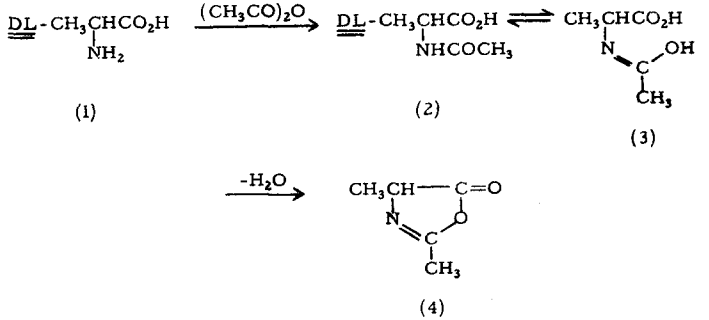
characteristics of this group make it suitable for peptide synthesis in both anhydrous and aqueous media. The blocking group is stable to conditions used in the azide peptide synthesis.

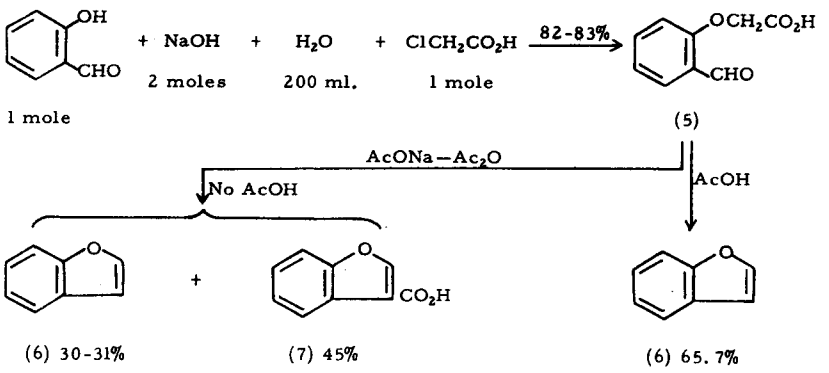
The Merck[3] total synthesis of ribonuclease involved coupling various peptide units to form a tetrahectapeptide (104 residues) known as S-protein. This polypeptide contains 8 cysteine and 3 methionine residues. The acetamidomethyl blocking group proved invaluable for protection of the cysteine units.

[1]A. Einhorn and C. Ladisch, *Ann.*, **343**, 265 (1905)
[2]D. F. Veber, J. D. Milkowski, R. G. Denkewalter, and R. Hirschmann, *Tetrahedron Letters*, 3057 (1968)
[3]R. G. Denkewalter, D. F. Veber, F. W. Holly, and R. Hirschmann, *Am. Soc.*, **91**, 502 (1969)

Acetic acid, CH_3CO_2H [1, 3, before **Acetic anhydride**]. Mol. wt. 60.05, b.p. 118°. An acetylation can sometimes be modified to advantage by use of acetic acid as a diluent. An efficient method of enzymic resolution illustrated for the case of DL-alanine (1) involves conversion to the DL-N-acetate (2) and enzymic hydrolysis to natural L-acetyl-N-alanine, an alcohol-soluble product easily separated from alcohol-insoluble L-alanine. The acetylation step presents the dificulty that, if the conditions are too severe, the N-acetyl derivative (2) may be converted in part through the enol (3) into the azlactone (4). A procedure for the precise control of the reaction[1] calls for heating 2 g. of DL-alanine and 5 ml. of acetic acid in a test tube to a little above 100°, and adding 3 ml. of acetic anhydride. The temperature falls (91–95°, cooling by added reagent), rises (100–103°, exothermal, acetylation), and begins to fall. Work-up affords DL-acetylalanine in nearly quantitative yield.

A procedure by Burgstahler and Worden[2] for the preparation of benzofurane (6) from *o*-formylphenoxyacetic acid (5) calls for refluxing for 8 hrs. a mixture of 0.5 mole of (5), 2.2 moles of sodium acetate, 450 ml. of acetic anhydride, and 450 ml. of acetic acid; benzofurane (6), the product of cyclodehydration and decarboxyla-

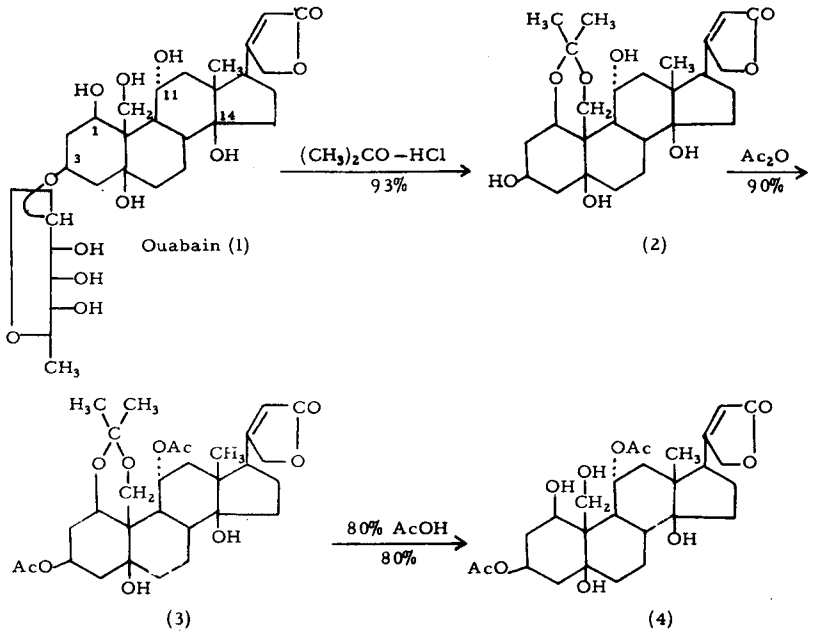




tion, was obtained in 65.7% yield. When no acetic acid was used, the yield of benzofurane was cut in half and coumarilic acid (7) was obtained in yield of 45%.

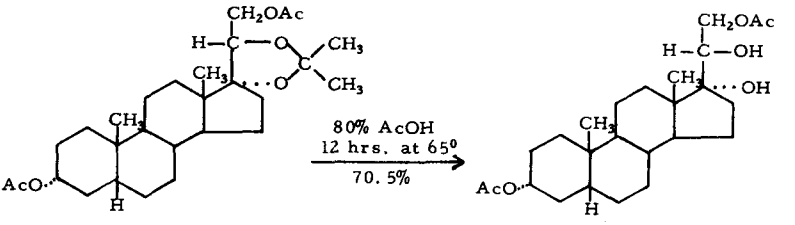
[1]L. F. Fieser, *Org. Expts.*, 138, D. C. Heath, second edition 1968
[2]A. W. Burgstahler and L. R. Worden, *Org. Syn.*, **46**, 28 (1966)

Acetic acid, 80% [**1**, 3, before **Acetic anhydride**]. Lewbart is credited by Reichstein *et al.*[1] with originating use of this reagent in an efficient and generally applicable method for the cleavage of acetonides, as illustrated by the Swiss workers in elucidating the structure of strogoside, a cardiac glycoside related to ouabain (1). Ouabain, a rhamnoside, had afforded only resins or extensive degradation products on attempted acid hydrolysis. Then Mannich and Siewart[2] found that although the glycoside is only sparingly soluble in acetone, when a suspension in acetone containing hydrogen chloride is shaken in the cold, the solid soon dissolves in the form of a



monoacetonide in which the group introduced is in the sugar residue. On standing for 1 or 2 weeks the solution deposits crystals of the 1,3-monoacetonide of ouabain. The Reichstein group applied this procedure to 24.25 g. of ouabain and obtained 14.44 g. of the 1,19-acetonide (2), and this on acetylation afforded the acetate-acetonide (3). Then a solution of 6 g. of (3) in 250 ml. of 80% acetic acid was let stand at 20° for 3 days and evaporated in vacuum; crystallization of the residue from water gave ouabagenin 3,11-diacetate (4) in 80% yield.

More recently, Lewbart[3] reported selective hydrolysis of the acetonide group of 17,20α-isopropylidenedioxy-5β-pregnane-3α,21-diol diacetate (5) with retention of the primary and secondary acetoxy groups.

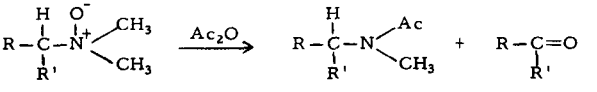


(5) (6)

[1]U. P. Geiger, Ek. Weiss, and T. Reichstein, *Helv.*, **50**, 194 (1967)
[2]C. Mannich and G. Siewart, *Ber.*, **75**, 737 (1942).
[3]M. L. Lewbart, *J. Org.*, **33**, 1695 (1968)

Acetic anhydride [bottom of **1**, 3].

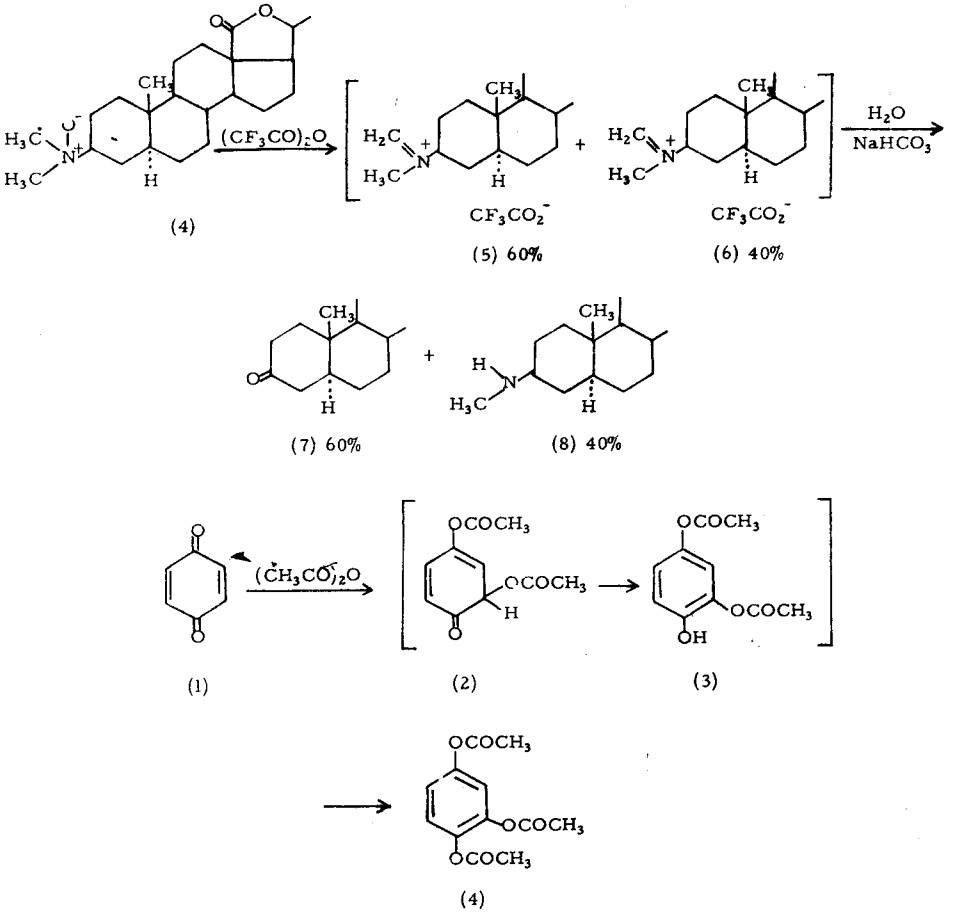
Polonovski reaction.[1] This reaction consists in the reaction of the N-oxide of a tertiary amine (1) with acetic anhydride to form the N-acylated secondary amine (2) as the major product and the deaminated ketone (3) as minor product:



(1) (2) (3)

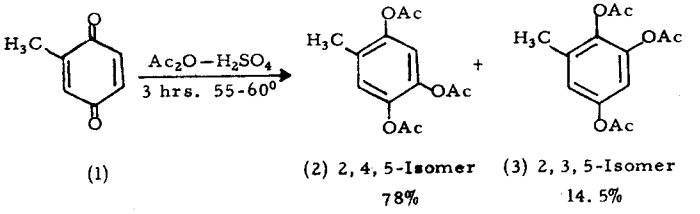
The mechanism of the Polonovski reaction has been studied without conclusive results.[2] Recently a French group[3] interested in steroidal alkaloids reasoned that trifluoroacetic anhydride might be more reactive and applied the reaction to (4), the N-oxide of N-methyldihydro-5α-paravallarine. NMR data provided evidence for the formation of the immonium salts (5) and (6). Hydrolysis with aqueous sodium bicarbonate leads to (7) and (8).

Thiele reaction. In a typical Thiele reaction,[4,5] 1,4-benzoquinone (1) is added with stirring at room temperature or below to a solution of a catalyst such as concentrated sulfuric acid in acetic anhydride; 1,4-addition to (2) is followed rapidly by enolization (3) and acetylation to give 1,2,4-triacetoxybenzene (4) in high yield. In a few cases Thiele used zinc chloride as catalyst but without apparent advantage. Boron trifluoride etherate would appear to be a more satisfactory Lewis acid since



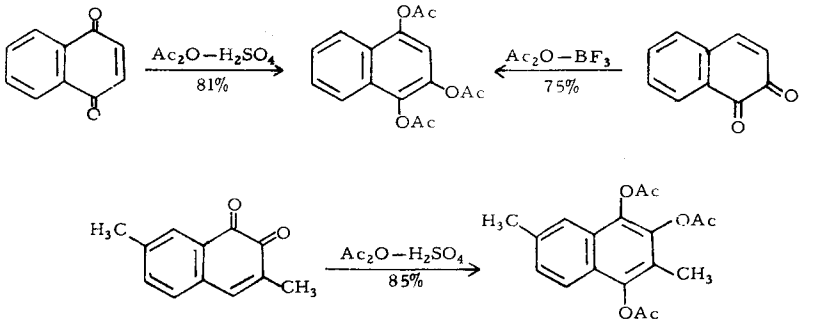
it is a liquid miscible with acetic anhydride; in one comparison a batch of 1,4-naphthoquinone gave 1,2,4-triacetoxynaphthalene in 81% yield with boron trifluoride etherate and in 74.5% yield with sulfuric acid as catalyst (Fieser[6] and *Reagents*, 1, 72).

The following discussion of catalysts and yields includes new observations by Wilgus and Gates[7] of the Eastman Kodak Co. Thus these investigators report that toluquinone (1) on reaction with acetic anhydride and sulfuric acid gives in 90% yield a mixture shown by VPC analysis to represent a yield of 78% of the 2,4,5-triacetoxy derivative (2) and a 14.5% yield of 2,3,5-isomer (3). Thus the reaction



involves attack by a new acetoxyl group in the positions *para* and *meta* to the methyl group originally present.

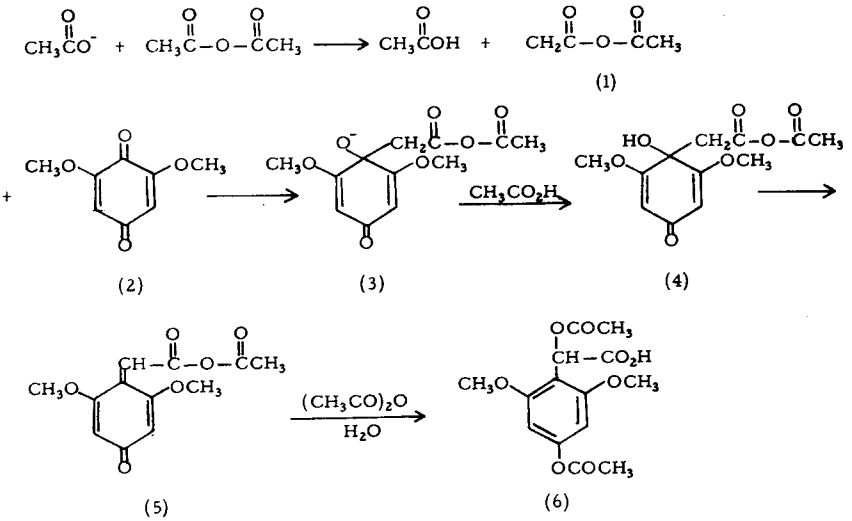
Data already summarized (*see* **1**, 71) show that with α-naphthoquinone, which is unhindered, BF_3-etherate is a more satisfactory catalyst for Thiele acetoxylation than sulfuric acid, but that with hindered quinones BF_3-etherate is a less potent catalyst than H_2SO_4. Thus 2,5-dimethyl-1,4-benzoquinone adds acetic anhydride smoothly in the presence of BF_3-etherate but 2,6-dimethyl-1,4-benzoquinone does not; on the other hand, 2,6-dimethyl-1,4-benzoquinone undergoes the H_2SO_4-catalyzed Thiele reaction. Fieser and Fieser's *Advanced Organic Chemistry*, p. 855, presents theoretical interpretations of the relationships noted and of the fact that 2-methyl-1,4-naphthoquinone is relatively inert to acetic anhydride–sulfuric acid. Wilgus and Gates[7] found that with BF_3-etherate catalysis 2-methyl-1,3,4-triacetoxynaphthalene is produced in 27% yield in a reaction period of 18 hrs. and in 52% yield in a period of 120 hrs. Burton and Praill (**1**, 801) found that perchloric acid is a more effective Thiele catalyst and that in the presence of this acid the hindered quinone reacts to give 2-methyl-1,3,4-triacetoxynaphthalene in moderate yield. A study of samples of 1,4-naphthoquinone of various grades of purity (**1**, 715–716) further demonstrated the efficacy of perchloric acid as catalyst for Thiele acetoxylation of the *p*-quinone. 1,2-Naphthoquinone shows about the same reactivity to Ac_2O—H_2SO_4 as does 1,4-naphthoquinone to Ac_2O—BF_3 (*Adv. Org. Chem.*,



p. 855). Thiele acetylation proceeds in good yield in spite of the presence of a methyl group adjacent to one of the quinonoid carbonyl groups.[8]

M. Lounasmaa,[9] of the Technical University of Helsinki, Otaniemi, Finland, refluxed for several hours a solution of 2,6-dimethoxy-1,4-benzoquinone in acetic anhydride in the presence of sodium acetate, added water, and isolated by extraction with chloroform and crystallization from acetic acid a colorless product melting at 149–150° which, on the basis of analysis ($C_{14}H_{16}O_8$), mass spectrography, and IR and NMR spectroscopy, was assigned the structure (6).

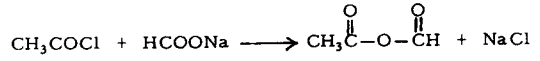
[1]M. Polonovski and M. Polonovski, *Bull. soc.*, [4] **39**, 147 (1926); **41**, 1190 (1927)
[2]E. Wenkert, *Experientia*, **10**, 346 (1954); R. Huisgen *et al.*, *Ber.*, **92**, 3223 (1959); **93**, 363 (1960); *idem*, *Tetrahedron Letters*, 783 (1965); S. Oae, T. Kitao, and Y. Kitaoka, *Am. Soc.*, **84**, 3366 (1962)
[3]A. Cavé, C. Kan-Fan, P. Potier, and J. Le Men, *Tetrahedron*, **23**, 4681 (1967)
[4]J. Thiele, *Ber.*, **31**, 1247 (1898)



[5]J. Thiele and E. Winter, *Ann.*, **311**, 341 (1899)
[6]L. F. Fieser, *Am. Soc.*, **70**, 3165 (1948)
[7]H. S. Wilgus, III, and J. W. Gates, Jr., *Canad. J. Chem.*, **45**, 1975 (1967)
[8]L. F. Fieser and A. M. Seligman, *Am. Soc.*, **56**, 2690 (1934). The yield here reported is that obtained by L. F. F. on repeating the experiment with 492 mg. of the quinone and a cold solution of 0.5 g. of sulfuric acid in 30 ml. of iced acetic anhydride. The product precipitated on addition of water amounted to 500 mg. (85%); crystallization from acetic acid gave white needles, m.p. 159°.
[9]M. Lounasmaa, *Tetrahedron Letters*, 91 (1968); *idem*, *Chem. Scand.*, **22**, 70 (1968)

Acetic–formic anhydride [1, 4] Mol. wt. 88.06.

[Line 16]: An improved preparatory procedure stated to be essentially that of Muramatsu *et al.*[4] is described as follows by Krimen.[6] A 2-l. three-necked flask equipped with stirrer, thermometer, reflux condenser with calcium chloride tube, and dropping tube is charged with 300 g. (4.41 moles) of finely ground sodium formate and 250 ml. of anhydrous ether (a slight excess of sodium formate ensures



a product free of acetyl chloride). The dropping tube is charged with 294 g. (266 ml., 3.75 moles) of acetyl chloride, a cooling bath (20–24°) is put in place to control the mildly exothermal reaction, and the acetyl chloride is run in in about 5 min. at a temperature controlled to 23–27°. The mixture is then stirred at 23–27° for 5.5 hrs. to ensure complete reaction. The mixture is then filtered by suction and the salt residue rinsed with ether. The ether is removed by distillation at reduced pressure, and distillation of the residue at reduced pressure gives 212 g. (65%) of colorless acetic–formic anhydride, b.p. 27–28°/10 mm., or 38–38.5°/39 mm., n_D^{20} 1.388.

The mixed anhydride may be stored at 4° in a standard round-bottomed flask fitted with a 24/40 polyethylene stopper. Since moisture catalyzes decomposition of the

product to acetic acid and carbon monoxide, it must not be stored in a sealed container.

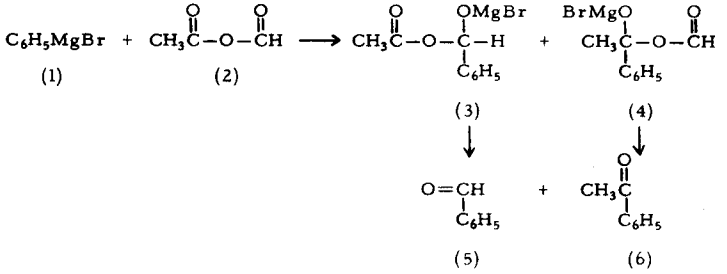
Spectrographic characterization.[6] The infrared spectrum of the mixed anhydride shows bands in the carbonyl region at 1765 and 1791 cm^{-1} and carbon–oxygen–carbon stretching absorption at 1050 cm^{-1} (a band at 1180 cm^{-1} could also be due to C—O—C). The NMR spectrum shows singlets at $\delta = 2.25$ (acetyl protons), and at $\delta = 9.05$ (formyl proton).

If the product is not pure, the following peaks may be observed from the impurity indicated:

$$\underline{H}COOH,\ \delta = 8.05;\ (\underline{H}CO)_2O,\ \delta = 8.85;\ C\underline{H}_3,\ \delta = 2.05;$$

$$CH_3CO_2\underline{H},\ \delta = 2.05;\ C\underline{H}_3COCl,\ \delta = 2.68;\ (C\underline{H}_3CO)_2O,\ \delta = 2.20.$$

Reaction with Grignard reagents. Edwards and Kammann[7] studied the reaction of phenylmagnesium bromide in ether at −70° with one equivalent of formic–acetic anhydride and found that the less hindered carbonyl group of the mixed anhydride reacts preferentially, with the result that the aldehydic product (5) predominates strongly over the methyl ketone (6). With ether as solvent, the ratio



(a)	Ether −70°	82.9	17.1	mole percent
(b)	THF −70°	53.5	46.5	
(c)	Ether 0°	84.0	16.0	

of products was nearly the same at 0° as at −70°. Use of tetrahydrofurane as solvent eliminated the preference, and the mole percent of aldehyde and that of methyl ketone were about the same. Aldehydes predominated strongly over ketones in the products obtained with four other aromatic Grignard reagents; less strongly with aliphatic reagents.

Blocking group in peptide synthesis. The conversion of an amino acid into its N-formyl derivative does not require preformed acetic–formic anhydride. Sheehan and Yang[5] added 83 ml. of acetic anhydride dropwise to a mixture of 0.10 mole of the amino acid in 250 ml. of 88% formic acid at a rate to maintain a temperature of 50–60°. The mixture was stirred at room temperature for 1 hr. and 80 ml. of ice water was added. The mixture was concentrated at reduced pressure and the crystalline residue could be crystallized easily from water or aqueous ethanol.

Formylation of amines and alcohols. Béhal,[8] discoverer of the reagent, found that it reacts unidirectionally with simple alcohols to produce alkyl formates free from acetates. Hurd *et al.*[9] found that acetic–formic anhydride (prepared from formic acid and ketene) reacts quantitatively with aniline to give formanilide. Another study[10] established that acetic-formic anhydride mixes endothermally with 2-nitro-2-methyl-1-propanol, exothermally with 2-nitro-2-methyl-1,3-propanediol, and displays no appreciable temperature effect with either 2-nitro-1-butanol or tris-(hydroxymethyl)-nitromethane. Formic esters are favored by avoiding a high reaction temperature and by not using sulfuric acid as catalyst. The mixed anhydride has been used for the preparation of formyl fluoride.[11]

Unhindered phenols are converted into formates in satisfactory yields.[12]

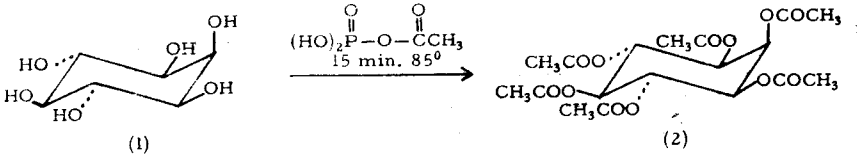
[6]L. I. Krimen, procedure submitted to *Org. Syn.*, 1967
[7]W. R. Edwards, Jr., and K. P. Kammann, Jr., *J. Org.*, **29**, 913 (1964)
[8]A. Béhal, *Compt. rend.*, **128**, 1460 (1900)
[9]C. D. Hurd and A. S. Roe, *Am. Soc.*, **61**, 3355 (1939)
[10]C. D. Hurd, S. S. Drake, and O. Fancher, *ibid.*, **68**, 789 (1946)
[11]G. A. Olah and S. J. Kuhn, *ibid.*, **82**, 2380 (1960)
[12]S. Sófuku, I. Muramatsu, and A. Hagitani, *Bull. Chem. Soc. Japan*, **40**, 2942 (1967)

Acetic-phosphoric anhydride, $HO-\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}-O-\overset{\overset{O}{\|}}{C}CH_3$. [**1**, 4, before **Acetoacetyl fluoride**].

Mol. wt. 136.01. Anhydrous phosphoric acid is available from Matheson Co., Chicago, or can be prepared by dissolving 113 g. of phorphorus pentoxide in 150 g. of orthophosphoric acid at 60–70°.[1] The resulting product is a liquid that crystallizes on standing (m.p. 42°). The crystalline material can be liquefied by brief heating at 60° (prolonged heating or higher temperatues lead to formation of polyphosphoric acid).

The mixed anhydride, useful as an acetylating reagent,[1] is prepared just before use by adding 1 ml. of anhydrous phosphoric acid to 4 ml. of acetic anhydride (mole ratio, 1 : 1.7) in a graduated cylinder and stirring until a homogeneous solution is obtained. The temperature usually rises to 50–55°.

Acetylation. Inositol (1), which has five equatorial and one axial hydroxyl group, was acetylated by stirring 20 g. with 200 ml. of the reagent at 85° for 15 min. followed by treatment with ice-water. This afforded 47 g. (97%) of almost pure



(1) (2)

inositol hexaacetate (2). Previously known methods of acetylation, including the powerful Fritz-Schenk reagent[2] (acetic anhydride and perchloric acid in ethyl acetate) had failed to provide an acetate from croconic acid (3). The new reagent, acetic–phosphoric anhydride, affords croconic acid diacetate (4) in good yield by the procedure formulated.

The reagent can be used also for the Thiele reaction, that is, acid-catalyzed addition of acetic anhydride to a quinone with further conversion into the hydroquinone