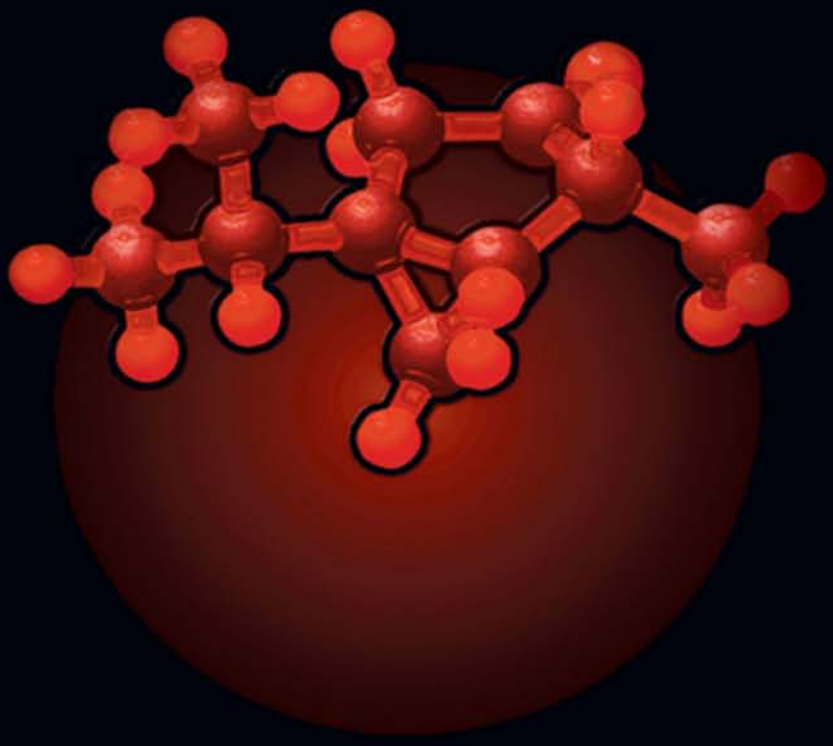

Handbook of Reagents for Organic Synthesis

Reagents for Heteroarene Functionalization

Edited by
André B. Charette

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General Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
BBN	borabicyclo[3.3.1]nonane
BCME	dis(chloromethyl)ether
BHT	butylated hydroxytoluene (2,6-di-*t*-butyl-*p*-cresol)
BINAL-H	2,2′-dihydroxy-1,1′-binaphthyl-lithium aluminum hydride
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2,2′-naphthol
bipy	2,2′-bipyridyl
BMS	borane–dimethyl sulfide
Bn	benzyl
Boc	*t*-butoxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
Bs	brosyl (4-bromobenzenesulfonyl)
BSA	*N,O*-bis(trimethylsilyl)acetamide
Bu	*n*-butyl
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
Cbz	benzyloxycarbonyl
CDI	*N,N*′-carbonyldiimidazole
CHIRAPHOS	2,3-bis(diphenylphosphino)butane
Chx	=Cy
cod	cyclooctadiene
cot	cyclooctatetraene
Cp	cyclopentadienyl
CRA	complex reducing agent
CSA	10-camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
Cy	cyclohexyl
d	density
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	*N,N*′-diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBAD	di-*t*-butyl azodicarboxylate
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*′-dicyclohexylcarbodiimide
DCME	dichloromethyl methyl ether
DDO	dimethyldioxirane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL	diisobutylaluminum hydride
DIEA	=DIPEA
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane
DIPEA	diisopropylethylamine
diphos	=dppe
DIPT	diisopropyl tartrate
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
dmg	dimethylglyoximato
DMPU	*N,N*′-dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio) sulfonium tetrafluoroborate
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DTBP	di-*t*-butyl peroxide
EDA	ethyl diazoacetate
EDC	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EDCI	=EDC
ee	enantiomeric excess
EE	1-ethoxyethyl
Et	ethyl
ETSA	ethyl trimethylsilylacetate
EWG	electron withdrawing group
Fc	ferrocenyl
Fmoc	9-fluorenylmethoxycarbonyl
fp	flash point
Hex	*n*-hexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
HOBt	l-hydroxybenzotriazole
HOBT	=HOBt
HOSu	*N*-hydroxysuccinimide
Im	imidazole (imidazolyl)
Ipc	isopinocampheyl
IR	infrared
KHDMS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LD_{50}	dose that is lethal to 50% of test subjects

LDA	lithium diisopropylamide
LDMAN	lithium 1-(dimethylamino)naphthalenide
LHMDS	=LiHMDS
LICA	lithium isopropylcyclohexylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
LTMP	=LiTMP
LTA	lead tetraacetate
lut	lutidine
m-CPBA	*m*-chloroperbenzoic acid
MA	maleic anhydride
MAD	methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide)
MAT	methylaluminum bis(2,4,6-tri-*t*-butylphenoxide)
Me	methyl
MEK	methyl ethyl ketone
MEM	(2-methoxyethoxy)methyl
MIC	methyl isocyanate
MMPP	magnesium monoperoxyphthalate
MOM	methoxymethyl
MoOPH	oxodiperoxomolybdenum(pyridine)-(hexamethylphosphoric triamide)
mp	melting point
MPM	=PMB
Ms	mesyl (methanesulfonyl)
MS	mass spectrometry; molecular sieves
MTBE	methyl *t*-butyl ether
MTM	methylthiomethyl
MVK	methyl vinyl ketone
n	refractive index
NaHDMS	sodium hexamethyldisilazide
Naph	naphthyl
NBA	*N*-bromoacetamide
nbd	norbornadiene (bicyclo[2.2.1]hepta-2,5-diene)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NORPHOS	bis(diphenylphosphino)bicyclo[2.2.1]-hept-5-ene
Np	=Naph
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pent	*n*-pentyl
Ph	phenyl
phen	1,10-phenanthroline
Phth	phthaloyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMDTA	*N,N,N′,N″,N″*-pentamethyldiethylene-triamine
PPA	polyphosphoric acid
PPE	polyphosphate ester
PPTS	pyridinium *p*-toluenesulfonate
Pr	*n*-propyl
PTC	phase transfer catalyst/catalysis
PTSA	*p*-toluenesulfonic acid
py	pyridine
RAMP	(R)-1-amino-2-(methoxymethyl)pyrrolidine
rt	room temperature
salen	bis(salicylidene)ethylenediamine
SAMP	(*S*)-1-amino-2-(methoxymethyl)pyrrolidine
SET	single electron transfer
Sia	siamyl (3-methyl-2-butyl)
TASF	tris(diethylamino)sulfonium difluorotrimethylsilicate
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAD	=DBAD
TBAI	tetrabutylammonium iodide
TBAP	tetrabutylammonium perruthenate
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide
TBS	=TBDMS
TCNE	tetracyanoethylene
TCNQ	7,7,8,8-tetracyanoquinodimethane
TEA	triethylamine
TEBA	triethylbenzylammonium chloride
TEBAC	=TEBA
TEMPO	2,2,6,6-tetramethylpiperidinoxyl
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran; tetrahydropyranyl
Thx	thexyl (2,3-dimethyl-2-butyl)
TIPS	triisopropylsilyl
TMANO	trimethylamine *N*-oxide
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Tol	*p*-tolyl
TPAP	tetrapropylammonium perruthenate
TBHP	*t*-butyl hydroperoxide
TPP	tetraphenylporphyrin
Tr	trityl (triphenylmethyl)
Ts	tosyl (*p*-toluenesulfonyl)
TTN	thallium(III) nitrate
UHP	urea–hydrogen peroxide complex
Z	=Cbz

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for Organic Synthesis

Reagents for Heteroarene Functionalization

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Reagents for Heteroarene Functionalization

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Contents

Preface

The eight-volume *Encyclopedia of Reagents for Organic Synthesis* (*EROS*), authored and edited by experts in the field, and published in 1995, had the goal of providing an authoritative multivolume reference work describing the properties and reactions of approximately 3000 reagents. With the coming of the Internet age and the continued introduction of new reagents to the field as well as new uses for old reagents, the electronic sequel, *e-EROS*, was introduced in 2002 and now contains in excess of 4000 reagents, catalysts, and building blocks, making it an extremely valuable reference work. At the request of the community, the second edition of the encyclopedia, *EROS-II*, was published in March 2009 and contains the entire collection of reagents at the time of publication in a 14-volume set.

While the comprehensive nature of *EROS* and *EROS-II* and the continually expanding *e-EROS* render them invaluable as reference works, their very size limits their practicability in a laboratory environment. For this reason, a series of inexpensive one-volume *Handbooks of Reagents for Organic Synthesis* (*HROS*), each focused on a specific subset of reagents, was introduced by the original editors of *EROS* in 1999:

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Oxidizing and Reducing Agents
Edited by Steven D. Burke and Rick L. Danheiser

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This series has continued over the last several years with the publication of a further series of *HROS* volumes, each edited by a current member of the *e-EROS* editorial board:

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This series now continues with the present volume entitled *Reagents for Heteroarene Functionalization*, edited by André Charette, long-standing member of the online e-EROS Editorial Board. This 15th volume in the *HROS* series, like its predecessors, is intended to be an affordable, practicable compilation of reagents arranged around a central theme that it is hoped will be found at arm's reach from synthetic chemists worldwide. The reagents have been selected to give broad relevance to the volume, within the limits defined by the subject matter. We have enjoyed putting this volume together and hope that our colleagues will find it just as enjoyable and useful to read and consult.

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Introduction

Heterocycles and, in particular, heteroarenes are among the most prevalent structural units in natural products, pharmaceuticals, agrochemicals, ligands for metal complexes, and electroactive organomaterials. Consequently, a plethora of synthetic methods has appeared over the years to not only facilitate construction of the heteroarene motif but also to enable further modifications employing the mildest conditions possible. Traditionally, unsubstituted heteroarenes have been functionalized via electrophilic aromatic substitution and regioselective metalation followed by electrophilic trapping/transition metal-catalyzed coupling and *N*-alkylation and *N*-arylation reactions. In the last two decades, intensive research efforts have been geared toward developing novel catalytic conditions for the site-selective formation of carbon–carbon and carbon–heteroatom bonds through direct heteroarene C–H functionalization. Heteroarenes are particularly good substrates in these reactions since they offer good regiocontrol due to the natural reactivity pattern of their various C–H bonds. Such research endeavors have produced a significant number of alternative procedures to complement traditional methods. In particular, impressive achievements have been reported using various late transition metal catalysts such as Pd, Ru, Rh, Cu, and Fe. These catalysts, in conjunction with another suitable coupling partner (e.g., halide, organometallic, and carboxylic acid), provide access to functionalized heteroarenes without requiring conventional double preactivation procedures (e.g., the protocols observed in Kumada, Suzuki–Miyaura, Stille, Hiyama, or Negishi coupling reactions). Moreover, direct C–H functionalization reactions often provide complementary regioselectivities compared with traditional derivatization reactions.

The development and application of selective C–H functionalization processes toward heteroarene synthesis is rapidly evolving. In 2006, the first *Handbook of Reagents for Organic Synthesis*, *Reagents for Direct Functionalization of C-H Bonds* (Ed. Philip L. Fuchs) was published by Wiley. This volume contained 80 reagents, which targeted a wide range of transformations and starting materials, including the formation of stereocenters. A search for the number of citations since 2006 for "C–H functionalization" produces a spectacular picture that describes this burgeoning field, forecasts its continual expansion, provided the opportunities to create and conceive novel synthetic methods, and illustrates its important role in redefining how organic chemists make molecules. Given this incredible burst in popularity of C–H functionalization, it has been a *tour de force* to develop a sizable Handbook to include all the key reagents developed in the last 10 years for only selective heteroarene functionalization reactions, comprising both traditional and transition metal-catalyzed C–H functionalization. Since these reactions typically involve one heteroarene, a coupling partner, and a catalyst, the Handbook not only focuses on the catalyst itself but also contains other key reaction species. To achieve this purpose, 117 reagents were selected, including 28 new reagents and 77 updated reagents. In order to cover the most important heteroarene C–H transformations in a single volume, the basic heteroarene cores of these reactions have been included and/or updated (e.g., pyridine, pyrazine, pyrrole, and *N*-methylindole). Furthermore, a supplementary list of relevant reagents that could not be included in this volume, but for which relevant articles can be found in *e-EROS*, is also provided.

As an additional resource to the reader for finding relevant information, a listing of Recent Reviews and Monographs follows this section.

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Recent Review Articles and Monographs

Selected Reviews

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Selected Books

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Short Note on InChIs and InChIKeys

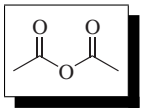
The IUPAC International Chemical Identifier (InChI™) and its compressed form, the InChIKey, are strings of letters representing organic chemical structures that allow for structure searching with a wide range of online search engines and databases such as Google and PubChem. While they are obviously an important development for online reference works, such as *Encyclopedia of Reagents for Organic Synthesis* (*e-EROS*), readers of this volume may be surprised to find printed InChI and InChIKey information for each of the reagents.

We introduced InChI and InChIKey to e-EROS in autumn 2009, including the strings in all HTML and PDF files. While we wanted to make sure that all users of *e-EROS*, the second print edition of *EROS*, and all derivative handbooks would find the same information, we appreciate that the strings will be of little use to the readers of the print editions, unless they treat them simply as reminders that *e-EROS* now offers the convenience of InChIs and InChIKeys, allowing the online users to make best use of their browsers and perform searches in a wide range of media.

If you would like to know more about InChIs and InChIKeys, please go to the *e-EROS* website: http://onlinelibrary.wiley.com/book/10.1002/047084289X and click on the InChI and InChIKey link.

A

Acetic Anhydride[1]



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InChI = 1/C4H6O3/c1-3(5)7-4(2)6/h1-2H3
InChIKey = WFDIJRYMOXRFFG-UHFFFAOYAH

(useful for the acetylation of alcohols,[2] amines,[3] and thiols,[4] oxidation of alcohols,[5] dehydration,[6] Pummerer[7] reaction, Perkin[8] reaction, Polonovski[9] reaction, *N*-oxide reaction,[10] Thiele[11] reaction, ether cleavage,[12] enol acetate formation,[13] *gem*-diacetate formation[14])

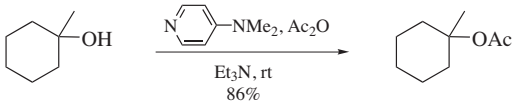
Physical Data: bp 138–140 °C; mp −73 °C; *d* 1.082 g cm^{-3}.
Solubility: sol most organic solvents. Reacts with water rapidly and alcohol solvents slowly.
Form Supplied in: commercially available in 98% and 99+% purities. Acetic anhydride-d_6 is also commercially available.
Analysis of Reagent Purity: IR, NMR.[15]
Preparative Methods: acetic anhydride is prepared industrially by the acylation of Acetic Acid with Ketene.[1b] A laboratory preparation of acetic anhydride involves the reaction of sodium acetate and Acetyl Chloride followed by fractional distillation.[16]
Purification: adequate purification is readily achieved by fractional distillation. Acetic acid, if present, can be removed by refluxing with CaC_2 or with coarse magnesium filings at 80–90 °C for 5 days. Drying and acid removal can be achieved by azeotropic distillation with toluene.[17]
Handling, Storage, and Precautions: acetic anhydride is corrosive and a lachrymator and should be handled in a fume hood.

Acetylation. The most notable use of acetic anhydride is for the acetylation reaction of alcohols,[2] amines,[3] and thiols.[4] Acids, Lewis acids, and bases have been reported to catalyze the reactions.

Alcohols. The most common method for acetate introduction is the reaction of an alcohol with acetic anhydride in the presence of pyridine.[2] Often, Pyridine is used as the solvent and reactions proceed nearly quantitatively (eq 1).

$$\mathrm{ROH} \xrightarrow[\text{pyridine}]{\mathrm{Ac_2O}} \mathrm{ROAc} \qquad (1)$$

If the reaction is run at temperatures lower than 20 °C, primary alcohols can be acetylated over secondary alcohols selectively.[18] Under these conditions, tertiary alcohols are not acylated. Most alcohols, including tertiary alcohols, can be acylated by the addition of DMAP (4-dimethylaminopyridine) and acetyl chloride to the reaction containing acetic anhydride and pyridine. In general, the addition of DMAP increases the rate of acylation by 10^4 (eq 2).[19]

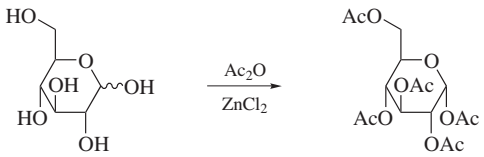


(2)

Recently, Vedejs found that a mixture of tributylphosphine and acetic anhydride acylates alcohols faster than acetic anhydride with DMAP.[20] However, the combination of acetic anhydride with DMAP and triethylamine proved superior. It is believed that the Et_3N prevents HOAc from destroying the DMAP catalyst.

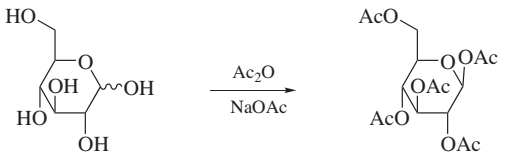
Tertiary alcohols have been esterified in good yield using acetic anhydride with calcium hydride or calcium carbide.[21] *t*-Butanol can be esterified to *t*-butyl acetate in 80% yield under these conditions. High pressure (15 kbar) has been used to introduce the acetate group using acetic anhydride in methylene chloride.[22] Yields range from 79–98%. Chemoselectivity is achieved using acetic anhydride and boron trifluoride etherate in THF at 0 °C. Under these conditions, primary or secondary alcohols are acetylated in the presence of phenols.[23]

α-D-Glucose is peracetylated readily using acetic anhydride in the presence of zinc chloride to give α-D-glucopyranose pentaacetate in 63–72% yield (eq 3).[24]



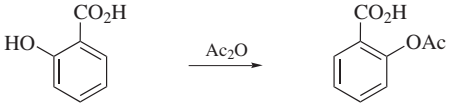
(3)

Under basic conditions, α-D-glucose can be converted into β-D-glucopyranose pentaacetate in 56% yield (eq 4).



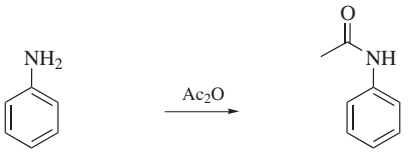
(4)

In the food and drug industry, high-purity acetic anhydride is used in the manufacture of aspirin by the acetylation of salicylic acid (eq 5).[25]



(5)

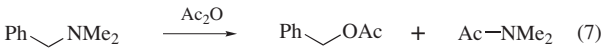
Amines. The acetylation of amines has been known since 1853 when Gerhardt reported the acetylation of aniline.[3] Acetamides are typically prepared by the reaction of the amine with acetic anhydride (eq 6).



(6)

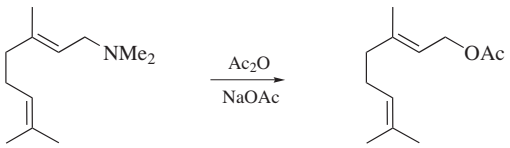
A unique method for selective acylation of secondary amines in the presence of primary amines involves the use of 18-Crown-6 with acetic anhydride and triethylamine.[26] It is believed that the 18-crown-6 complexes primary alkylammonium salts more tightly than the secondary salts, allowing selective acetylation.

In some cases, tertiary amines undergo a displacement reaction with acetic anhydride. A simple example involves the reaction of benzyldimethylamine with acetic anhydride to give dimethylacetamide and benzylacetate (eq 7).[27]



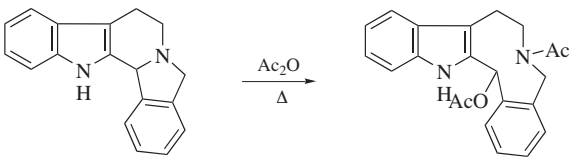
(7)

Allylic tertiary amines can be displaced by the reaction of acetic anhydride and sodium acetate.[28] The allylic acetate is the major product, as shown in eq 8.



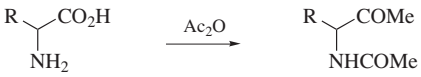
(8)

Cyclic benzylic amines may undergo ring opening upon heating with acetic anhydride (eq 9).[29]



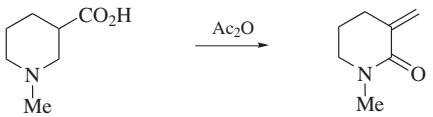
(9)

α-Amino acids react with acetic anhydride in the presence of a base to give 2-acetamido ketones.[30] This reaction is known as the Dakin–West reaction (eq 10) and is believed to go through a oxazolone mechanism. The amine base of choice is 4-dimethylaminopyridine. Under these conditions, the reaction can be carried out at room temperature in 30 min.



(10)

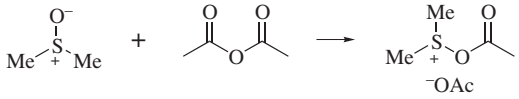
Cyclic β-amino acids rearrange to α-methylene lactams upon treatment with acetic anhydride, as shown in eq 11.[31]



(11)

Thiols. *S*-Acetyl derivatives can be prepared by the reaction of acetic anhydride and a thiol in the presence of potassium bicarbonate.[4] Several disadvantages to the *S*-acetyl group in peptide synthesis include β-elimination upon base-catalyzed hydrolysis. Also, sulfur to nitrogen acyl migration may be problematic.

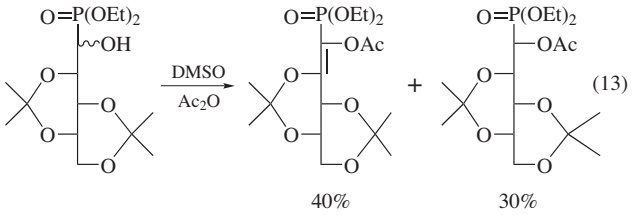
Oxidation. The oxidation of primary and secondary alcohols to the corresponding carbonyl compounds can be achieved using dimethyl sulfoxide–acetic anhydride.[5] The reaction proceeds through an acyloxysulfonium salt as the oxidizing agent (eq 12).



(12)

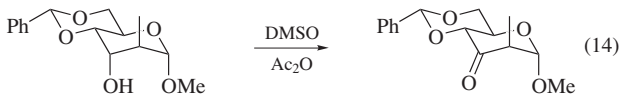
The oxidations often proceed at room temperature, although long reaction times (18–24 h) are sometimes required. A side product is formation of the thiomethyl ethers obtained from the Pummerer rearrangement.

If the alcohol is unhindered, a mixture of enol acetate (from ketone) and acetate results (eq 13).[32]



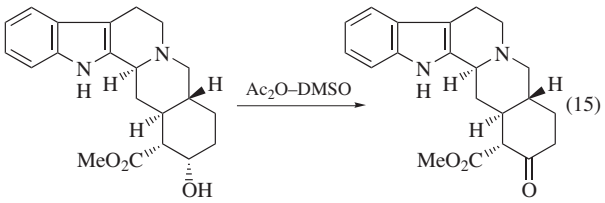
(13)

The oxidation of carbohydrates can be achieved by this method, as Hanessian showed (eq 14).[33]



(14)

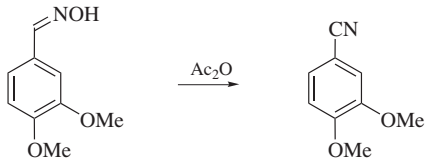
Aromatic α-diketones can be prepared from the acyloin compounds; however, aliphatic diketones cannot be prepared by this method.[34] The reaction proceeds well in complex systems without epimerization of adjacent stereocenters, as in the yohimbine example (eq 15).[35] This method compares favorably with that of dimethyl sulfoxide–dicyclohexylcarbodiimide.



(15)

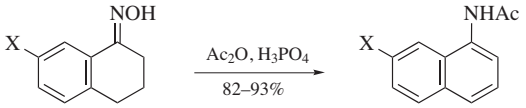
Dehydration. Many functionalities are readily dehydrated upon reaction with acetic anhydride, the most notable of which is the oxime.[6] Also, dibasic acids give cyclic anhydrides or ketones, depending on ring size.[36]

An aldoxime is readily converted to the nitrile as shown in eq 16.[37]



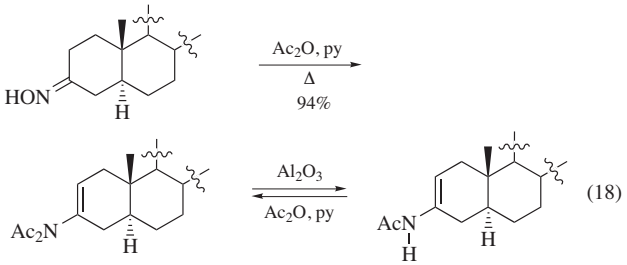
(16)

When oximes of α-tetralones are heated in acetic anhydride in the presence of anhydrous phosphoric acid, aromatization occurs as shown in eq 17.[38]



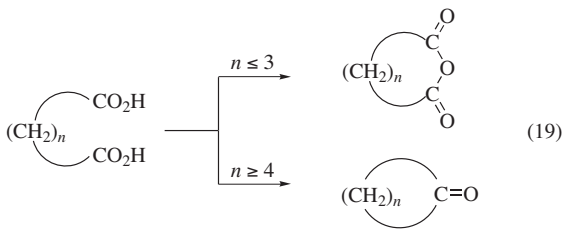
(17)

Oximes of aliphatic ketones lead to enamides upon treatment with acetic anhydride–pyridine, as shown in the steroid example in eq 18.[39]



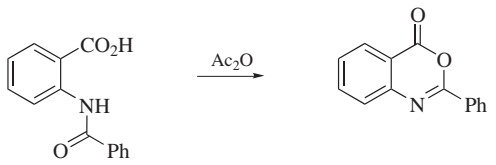
(18)

Upon heating with acetic anhydride, dibasic carboxylic acids lead to cyclic anhydrides of ring size 6 or smaller. Diacids longer than glutaric acid lead to cyclic ketones (eq 19).[36]



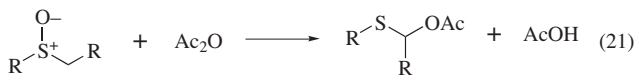
(19)

N-Acylanthranilic acids also cyclize when heated with acetic anhydride (eq 20). The reaction proceeds in 81% yield with slow distillation of the acetic acid formed.[40]



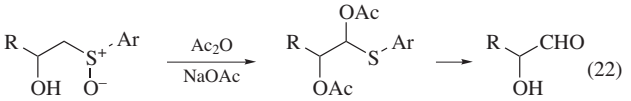
(20)

Pummerer Reaction. In 1910, Pummerer[7] reported that sulfoxides react with acetic anhydride to give 2-acetoxy sulfides (eq 21). The sulfoxide must have one α-hydrogen. Alternative reaction conditions include using trifluoroacetic anhydride and acetic anhydride.



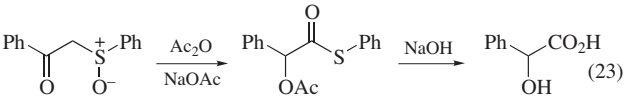
(21)

β-Hydroxy sulfoxides undergo the Pummerer reaction upon addition of sodium acetate and acetic anhydride to give α,β-diacetoxy sulfides. These compounds are easily converted to α-hydroxy aldehydes (eq 22).[41]



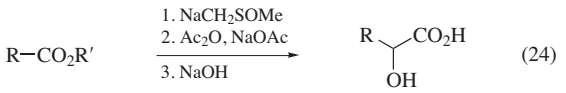
(22)

2-Phenylsulfonyl ketones rearrange in the presence of acetic anhydride–sodium acetate in toluene at reflux to give *S*-aryl thioesters (eq 23).[42] Upon hydrolysis, an α-hydroxy acid is obtained.



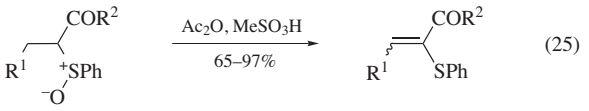
(23)

In the absence of sodium acetate, 2-phenylsulfonyl ketones give the typical Pummerer product. Since β-keto sulfoxides are available by the reaction of esters with the dimsyl anion, this overall process leads to one-carbon homologated α-hydroxy acids from esters (eq 24).[42]



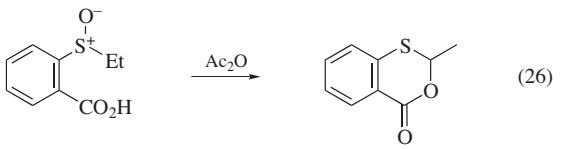
(24)

Also, 2-phenylsulfonyl ketones can be converted to α-phenylthio-α,β-unsaturated ketones via the Pummerer reaction using acetic anhydride and a catalytic amount of methanesulfonic acid (eq 25).[43]



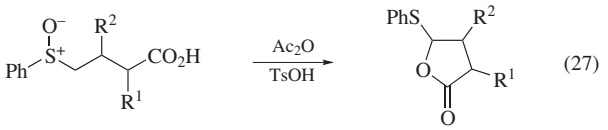
(25)

The Pummerer reaction has been used many times in heterocyclic synthesis as shown in eq 26.



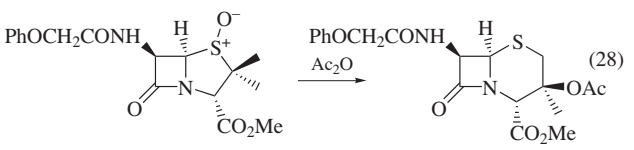
(26)

The Pummerer rearrangement of 4-phenylsulfinylbutyric acid with acetic anhydride in the presence of p-toluenesulfonic acid leads to butanolide formation (eq 27).[44] Oxidation with m-chloroperbenzoic acid followed by thermolysis then leads to an unsaturated compound.



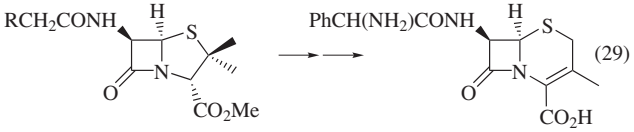
(27)

An unusual Pummerer reaction takes place with penicillin sulfoxide, leading to a ring expansion product as shown in eq 28.[45]



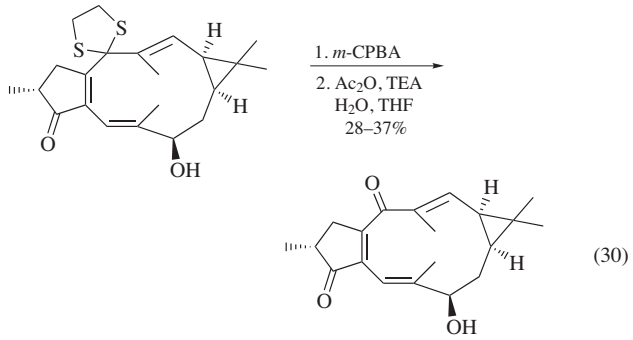
(28)

This led to discovery of the conversion of penicillin V and G to cephalexin,[46] a broad spectrum orally active antibiotic (eq 29).



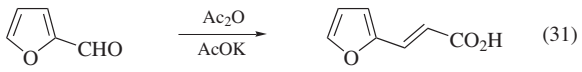
(29)

A Pummerer-type reaction was carried out on a dithiane protecting group to liberate the corresponding ketone (eq 30).[47] These were the only reaction conditions which provided any of the desired ketone.



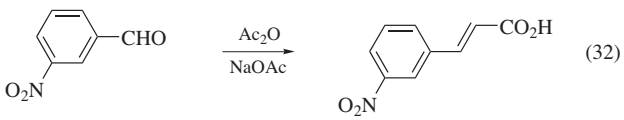
(30)

Perkin Reaction. The Perkin reaction,[8] developed by Perkin in 1868, involves the condensation of an anhydride and an aldehyde in the presence of a weak base to give an unsaturated acid (eq 31).



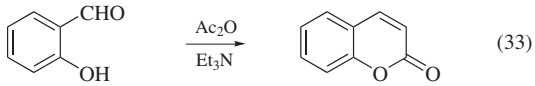
(31)

The reaction is often used for the preparation of cinnamic acids in 74–77% yield (eq 32).



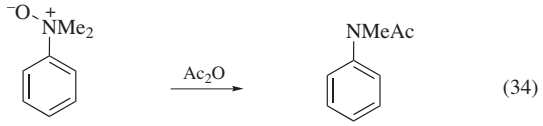
(32)

Aliphatic aldehydes give low or no yields of acid. Coumarin can be prepared by a Perkin reaction of salicylaldehyde and acetic anhydride in the presence of triethylamine (eq 33).



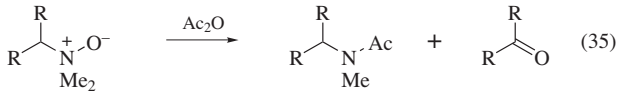
(33)

Polonovski Reaction. In the Polonovski reaction,[9] tertiary amine oxides react with acetic anhydride to give the acetamide of the corresponding secondary amine (eq 34).



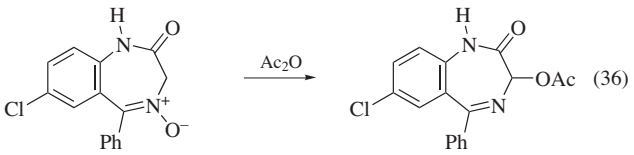
(34)

In nonaromatic cases, the Polonovski reaction gives the *N*-acylated secondary amine as the major product and the deaminated ketone as a minor product (eq 35).[48]



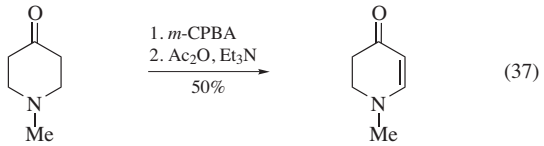
(35)

This reaction has been extended to a synthesis of 2-acetoxybenzodiazepine via an *N*-oxide rearrangement (eq 36).



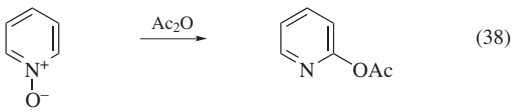
(36)

An application of the Polonovski reaction forms β-carbonylenamines. *N*-Methylpiperidone is reacted with *m*-CPBA followed by acetic anhydride and triethylamine to give the β-carbonyl enamine (eq 37).[49]



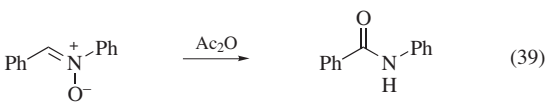
(37)

Reaction with *N*-Oxides. Pyridine 1-oxide reacts with acetic anhydride to produce 2-acetoxypyridine, which can be hydrolyzed to 2-pyridone (eq 38).[10]



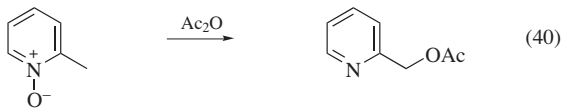
(38)

Open chain *N*-oxides, in particular nitrones, rearrange to amides (almost quantitatively) under acetic anhydride conditions (eq 39).[50]



(39)

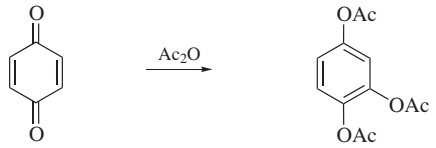
Heteroaromatic *N*-oxides with a side chain react with acetic anhydride to give side-chain acyloxylation (eq 40).[51]



(40)

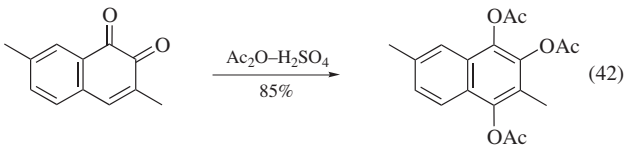
This reaction has been used in synthetic chemistry as the method of choice to form heterocyclic carbinols or aldehydes.

Thiele Reaction. The Thiele reaction converts 1,4-benzoquinone to 1,2,4-triacetoxybenzene using acetic anhydride and a catalytic amount of sulfuric acid.[11] Zinc chloride has been used without advantage. In this reaction, 1,4-addition to the quinone is followed by enolization and acetylation to give the substituted benzene (eq 41).



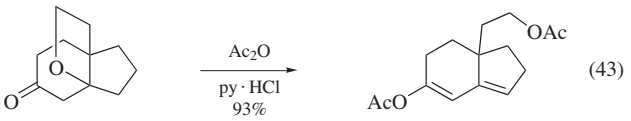
(41)

With unhindered quinones, BF_3 etherate is a more satisfactory catalyst but hindered quinones require the more active sulfuric acid catalyst. 1,2-Naphthoquinones undergo the Thiele reaction with acetic anhydride and sulfuric acid or boron trifluoride etherate (eq 42).



(42)

Ether Cleavage. Dialkyl ethers can be cleaved with acetic anhydride in the presence of pyridine hydrochloride or anhydrous Iron(III) Chloride. In both cases, acetate products are produced. As shown in eq 43, the tricyclic ether is cleaved by acetic anhydride and pyridine hydrochloride to give the diacetate in 93% yield.[12]

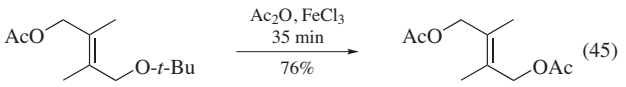


(43)

Simple dialkyl ethers react with iron(III) chloride and acetic anhydride to produce compounds where both R groups are converted to acetates (eq 44).[52]

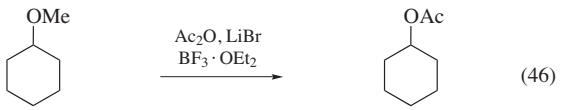
(44)

Cleavage of allylic ethers can occur using acetic anhydride in the presence of iron(III) chloride (eq 45). The reaction takes place without isomerization of a double bond, but optically active ethers are cleaved with substantial racemization.[53]



(45)

Cleavage of aliphatic ethers occurs with the reaction of acetic anhydride, boron trifluoride etherate, and lithium bromide (eq 46). The ethers are cleaved to the corresponding acetoxy compounds contaminated with a small amount of unsaturated product.[54] In some cases, the lithium halide may not be necessary.

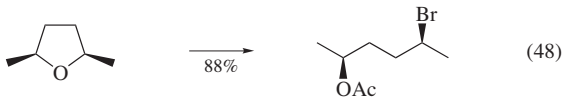


(46)

Cyclic ethers are cleaved to ω-bromoacetates using Magnesium Bromide and acetic anhydride in acetonitrile (eq 47).[55]

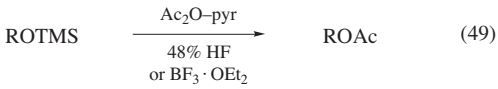
(47)

The reaction occurs with inversion of configuration, as shown in eq 48.



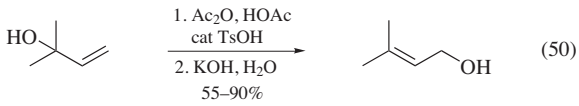
(48)

Trimethylsilyl ethers are converted to acetates directly by the action of acetic anhydride–pyridine in the presence of 48% HF or boron trifluoride etherate (eq 49).[56]



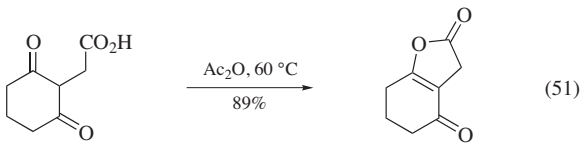
(49)

Miscellaneous Reactions. Primary allylic alcohols can be prepared readily by the action of *p*-toluenesulfonic acid in acetic anhydride–acetic acid on the corresponding tertiary vinyl carbinol, followed by hydrolysis of the resulting acetate.[57] The vinyl carbinol is readily available from the reaction of a ketone with a vinyl Grignard reagent. Overall yields of allylic alcohols are very good (eq 50).



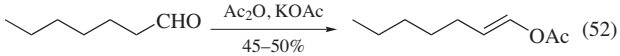
(50)

Enol lactonization occurs readily on an α-keto acid using acetic anhydride at elevated temperatures.[58] The reaction shown in eq 51 proceeds in 89% yield. In general, acetic anhydride is superior to acetyl chloride in this reaction.[59]



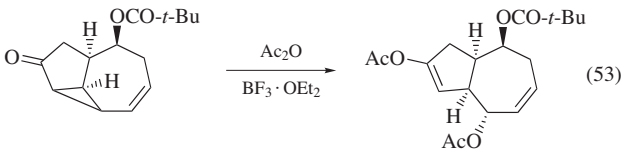
(51)

Aliphatic aldehydes are easily converted to the enol acetate using acetic anhydride and potassium acetate (eq 52).[13] This reaction only works for aldehydes and is the principal reason for the failure of aldehydes to succeed in the Perkin reaction. Triethylamine and DMAP may also catalyze the reaction.



(52)

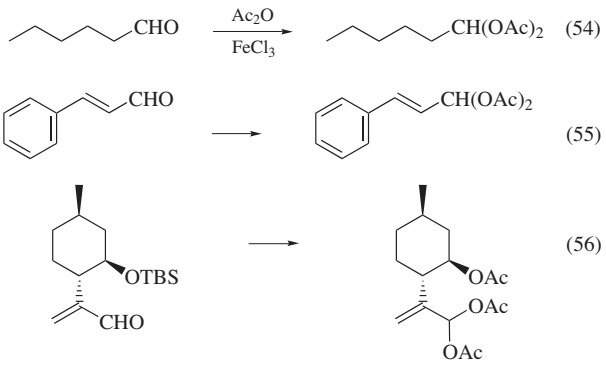
A cyclopropyl ketone is subject to homoconjugate addition using acetic anhydride/boron trifluoride etherate. Upon acetate addition, the enol is trapped as its enol acetate (eq 53).[60]



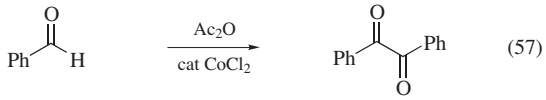
(53)

When an aldehyde is treated with acetic anhydride/anhydrous iron(III) chloride, geminal diacetates are formed in good to excellent yields.[14] Aliphatic and unsaturated aldehydes can be used

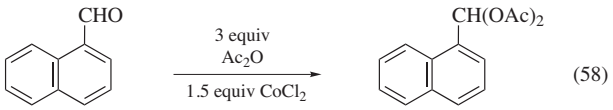
in this reaction as shown in eqs 54–56. Interestingly, if an α-hydrogen is present in an unsaturated aldehyde, elimination of the geminal diacetate product gives a 1-acetoxybutadiene.



If an aldehyde is treated with acetic anhydride in the presence of a catalytic amount of cobalt(II) chloride, a diketone is formed (eq 57).[61]

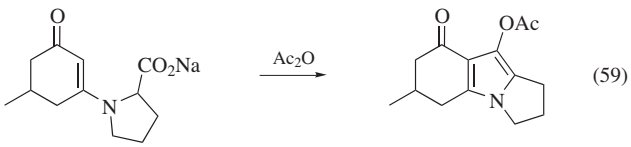


However, if 1.5 equiv of cobalt(II) chloride is added, the geminal diacetate is formed (eq 58).[62]

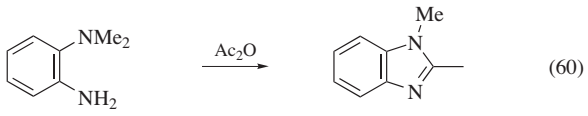


Apparently, the reaction in eq 58 occurs only when the starting material is polyaromatic or with compounds whose carbonyl IR frequency is less than 1685 cm^{-1}.

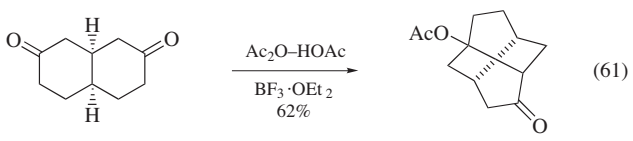
Acetic anhydride participates in several cyclization reactions. For example, enamines undergo a ring closure when treated with acetic anhydride (eq 59).[63]



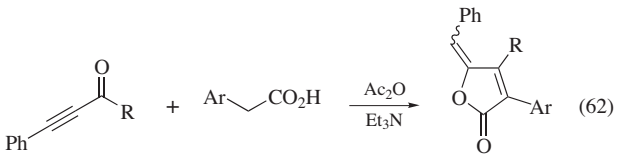
o-Diamine compounds also cyclize when treated with acetic anhydride (eq 60).[64]



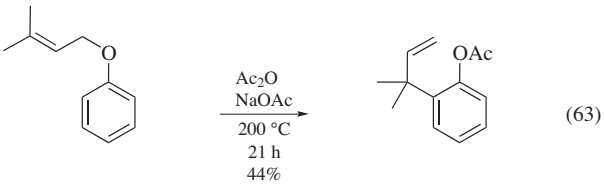
Twistane derivatives were obtained by the reaction of a decalindione with acetic anhydride, acetic acid, and boron trifluoride etherate (eq 61).[65]



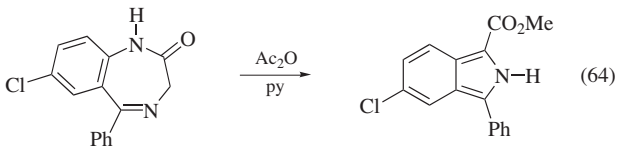
A condensation/cyclization reaction between an alkynyl ketone and a carboxylic acid in the presence of acetic anhydride/triethylamine gives a butenolide (eq 62).[66]



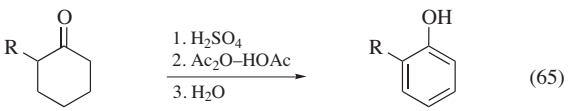
A few rearrangement reactions take place with acetic anhydride. A Claisen rearrangement is involved in the formation of the aromatic acetate in eq 63.[67] The reaction proceeds in 44% yield even after 21 h at 200 °C.



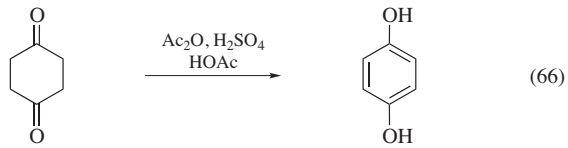
Complex rearrangements have occured using acetic anhydride under basic conditions, as shown in eq 64.[68]



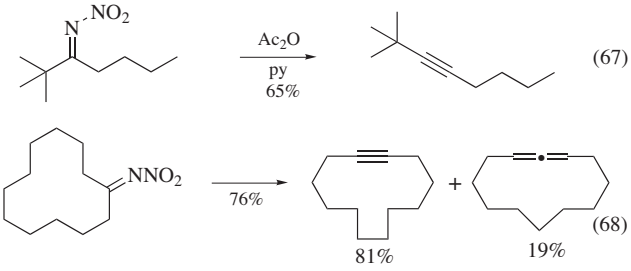
Aromatization occurs readily using acetic anhydride. Aromatization of α-cyclohexanones occurs under acidic conditions to lead to good yields of phenols (eq 65).[69] However, in totally unsubstituted ketones, aldol products are formed.



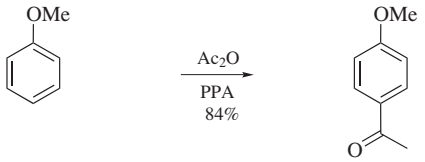
Aromatization of 1,4- and 1,2-cyclohexanediones leads to cresol products (eq 66) in over 90% yield.[70]



Alkynes and allenes are formed by the acylation of nitrimines using acetic anhydride/pyridine with DMAP as catalyst (eqs 67 and 68).[71] Nitrimines are prepared by nitration of ketoximes with nitrous acid.



Lastly, acetic anhydride participates in the Friedel–Crafts reaction.[72] Polyphosphoric acid is both reagent and solvent in these reactions (eq 69).



(69)

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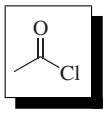
Acetyl Chloride[1]



[75-36-5] C_2H_3ClO (MW 78.50)
InChI = 1/C2H3ClO/c1-2(3)4/h1H3
InChIKey = WETWJCDKMRHUPV-UHFFFAOYAQ

(useful for electrophilic acetylation of arenes,[2] alkenes,[2a,3] alkynes,[4] saturated alkanes,[3a,5] organometallics, and enolates (on C or O);[6] for cleavage of ethers;[7] for esterification of sterically unhindered[8] or acid-sensitive[9] alcohols; for generation of solutions of anhydrous hydrogen chloride in methanol;[10] as a dehydrating agent; as a solvent for organometallic reactions;[11] for deoxygenation of sulfoxides;[12] as a scavenger for chlorine[13] and bromine;[14] as a source of ketene; and for nucleophilic acetylation[15])

Physical Data: bp 51.8 °C;[1a] mp −112.9 °C;[1a] *d* 1.1051 g cm^{-3};[1a] refractive index 1.38976.[1b] IR (neat) ν 1806.7 cm^{-1};[16] ^1H NMR ($CDCl_3$) δ 2.66 ppm; ^{13}C NMR ($CDCl_3$) δ 33.69 ppm (q) and 170.26 ppm (s); the bond angles (determined by electron diffraction[17]) are 127.5° (O–C–C), 120.3° (O–C–Cl), and 112.2° (Cl–C–C).

Analysis of Reagent Purity: a GC assay for potency has been described;[18] to check qualitatively for the presence of HCl, a common impurity, add a few drops of a solution of crystal violet in chloroform;[19] a green or yellow color indicates that HCl is present, while a purple color that persists for at least 10 min indicates that HCl is absent.[1b]

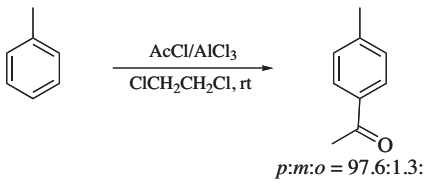
Preparative Methods: treatment of acetic acid or sodium acetate with the standard inorganic chlorodehydrating agents (PCl_3,[1b,23] SO_2Cl_2,[1a,24] or $SOCl_2$[1b,25]) generates material that may contain phosphorus- or sulfur-containing impurities.[1b,23a,26] Inorganic-free material can be prepared by treatment of HOAc with $Cl_2CHCOCl$ (Δ; 70%),[27] PhCOCl (Δ; 88%),[28] $PhCCl_3$ (cat. H_2SO_4, 90 °C; 92.5%),[29] or phosgene[30] (optionally catalyzed by DMF,[30e] magnesium or other metal salts,[30a,b,d] or activated carbon[30b,c]), or by addition of hydrogen chloride to acetic anhydride (85–90 °C; 'practically quantitative').[1a,31]

Purification: HCl-free material can be prepared either by distillation from dimethylaniline[11c,20] or by standard degassing procedures.[20c,21]

Handling, Storage, and Precautions: acetyl chloride should be handled only in a well-ventilated fume hood since it is volatile and toxic via inhalation.[22] It should be stored in a sealed container under an inert atmosphere. Spills should be cleaned up by covering with aq sodium bicarbonate.[1a]

Friedel–Crafts Acetylation. Arenes undergo acetylation to afford aryl methyl ketones on treatment with acetyl chloride (AcCl) together with a Lewis acid, usually aluminum chloride$_3$. This reaction, known as the Friedel–Crafts acetylation, is valuable as a preparative method because a single positional isomer is produced from arenes that possess multiple unsubstituted electron-rich positions in many instances.

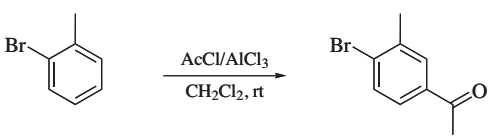
For example, Friedel–Crafts acetylation of toluene ($AcCl/AlCl_3$, ethylene dichloride, rt) affords *p*-methylacetophenone predominantly (*p*:*m*:*o* = 97.6:1.3:1.2; eq 1).[32]



(1)

Acetylation of chlorobenzene under the same conditions affords *p*-chloroacetophenone with even higher selectivity (*p*:*m* = 99.5:0.5).[33] Acetylation of bromobenzene[33] and fluorobenzene[33] afford the *para* isomers exclusively. The *para*:*meta*[34] and *para*:*ortho*[32,34] selectivities exhibited by $AcCl/AlCl_3$ are greater than those exhibited by most other Friedel–Crafts electrophiles.

Halogen substituents can be used to control regioselectivity. For example, by introduction of bromine *ortho* to methyl, it is possible to realize '*meta* acetylation of toluene' (eq 2).[35]



(2)

Regioselectivity is quite sensitive to reaction conditions (e.g. solvent, order of addition of the reactants, concentration, and

temperature). For example, acetylation of naphthalene can be directed to produce either a 99:1 mixture of C-1:C-2 acetyl derivatives (by addition of a solution of arene and AcCl in CS_2 to a slurry of $AlCl_3$ in CS_2 at 0 °C) or a 7:93 mixture (by addition of the preformed AcCl/$AlCl_3$ complex in dichloroethane to a dilute solution of the arene in dichloroethane at rt).[36] Similarly, acetylation of 2-methoxynaphthalene can be directed to produce either a 98:2 mixture of C-1:C-6 acetyl derivatives (using the former conditions) or a 4:96 mixture (by addition of the arene to a solution of the preformed AcCl/$AlCl_3$ complex in nitrobenzene).[37] Also, acetylation of 1,2,3-mesitylene can be directed to produce either a 100:0 mixture of C-4:C-5 isomers or a 3:97 mixture.[36c]

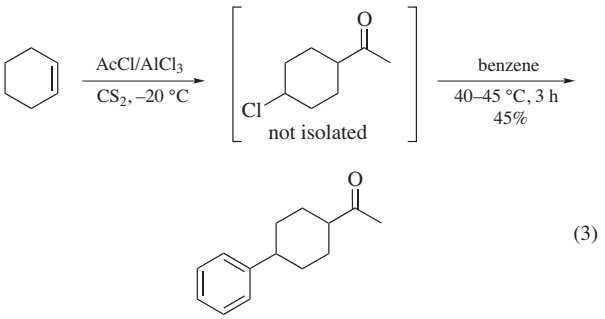
Frequently, regioselectivity is compromised by side reactions catalyzed by the HCl byproduct. For example, acetylation of *p*-xylene by treatment with $AlCl_3$ followed by Ac_2O (CS_2, Δ, 1 h) produces a 69:31 mixture of 2,5-dimethylacetophenone and 2,4-dimethylacetophenone, formation of the latter being indicative of competitive acid-catalyzed isomerization of *p*-xylene to *m*-xylene.[38] Also, although acetylation of anthracene affords 9-acetylanthracene regioselectively, if the reaction mixture is allowed to stand for a prolonged time prior to work-up (rt, 20 h) isomerization to a mixture of C-1, C-2, and C-9 acetyl derivatives occurs.[39]

These side reactions can be minimized by proper choice of reaction conditions. Isomerization of the arene can be suppressed by adding the arene to the preformed AcCl/$AlCl_3$ complex. This order of mixing is known as the 'Perrier modification' of the Friedel–Crafts reaction.[40] Acetylation of *p*-xylene using this order of mixing affords 2,5-dimethylacetophenone exclusively.[38] Isomerization of the product aryl methyl ketone can be suppressed by crystallizing the product out of the reaction mixture as it is formed. For example, on acetylation of anthracene in benzene at 5–10 °C, 9-acetylanthracene crystallizes out of the reaction mixture (as its 1/1 $AlCl_3$ complex) in pure form.[39] Higher yields of purer products can also be obtained by substituting zirconium(IV) chloride[41] or tin(IV) chloride[42] for $AlCl_3$.

AcCl is not well suited for industrial scale Friedel–Crafts acetylations because it is not commercially available in bulk (only by the drum) and therefore must be prepared on site.[1] The combination of acetic anhydride and anhydrous hydrogen fluoride, both of which are available by the tank car, is claimed to be more practical.[43] On laboratory scale, AcCl/$AlCl_3$ is more attractive than Ac_2O/HF or Ac_2O/$AlCl_3$. Whereas one equivalent of $AlCl_3$ is sufficient to activate AcCl, 1.5–2 equiv $AlCl_3$ (relative to arene) are required to activate Ac_2O.[36a,37b,38,44] Thus, with Ac_2O, greater amounts of solvent are required and temperature control during the quench is more difficult. Also, slightly lower isolated yields have been reported with Ac_2O than with AcCl in two cases.[36a,45] However, it should be noted that the two reagents generally afford similar ratios of regioisomers.[36a,38,46]

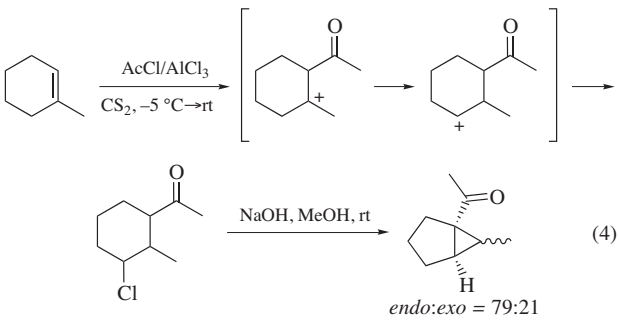
Acetylation of Alkenes. Alkenes, on treatment with AcCl/$AlCl_3$ under standard Friedel–Crafts conditions, are transformed into mixtures of β-chloroalkyl methyl ketones, allyl methyl ketones, and vinyl methyl ketones, but the reaction is not generally preparatively useful because both the products and the starting alkenes are unstable under the hyperacidic reaction conditions. Preparatively useful yields have been reported only with electron poor alkenes such as ethylene (dichloroethane, 5–10 °C; >80% yield of 4-chloro-2-butanone)[47] and allyl chloride (CCl_4, rt; 78% yield of 5-chloro-4-methoxy-2-pentanone after methanolysis),[48] which are relatively immune to the effects of acid.

The acetylated products derived from higher alkenes are susceptible to protonation or solvolysis which produces carbenium ions that undergo Wagner–Meerwein hydride migrations.[49] For example, on subjection of cyclohexene to standard Friedel–Crafts acetylation conditions (AcCl/$AlCl_3$, CS_2 −18 °C), products formed include not only 2-chlorocyclohexyl methyl ketone (in 40% yield)[50] but also 4-chlorocyclohexyl methyl ketone.[2a,51] If benzene is added to the crude acetylation mixture and the temperature is then increased to 40–45 °C for 3 h, 4-phenylcyclohexyl methyl ketone is formed in 45% yield (eq 3).[49a,b]



(3)

Wagner–Meerwein rearrangement also occurs during acetylation of methylcyclohexene, even though the rearrangement is anti-Markovnikov (β-tertiary → γ-secondary; eq 4).[52] Acetylation of *cis*-decalin[53] also produces a β-tertiary carbenium ion that undergoes anti-Markovnikov rearrangement. The rearrangement is terminated by intramolecular *O*-alkylation of the acetyl group by the γ-carbenium ion to form a cyclic enol ether in two cases.[49c,53]



(4)

Higher alkenes themselves are also susceptible to protonation. The resulting carbenium ions decompose by assorted pathways including capture of chloride (with $SnCl_4$ as the catalyst),[51,54] addition to another alkene to form dimer or polymer,[5b,55] proton loss (resulting in *exo*/*endo* isomerization), or skeletal rearrangement.[56]

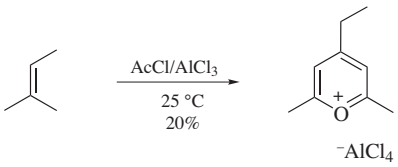
Higher alkenes can be acetylated in synthetically useful yield by treatment with AcCl together with various mild Lewis acids. One that deserves prominent mention is ethylaluminum dichloride (CH_2Cl_2, rt), which is useful for acetylation of all classes of alkenes (monosubstituted, 1,2-disubstituted, and trisubstituted).[57] For example, cyclohexene is converted into an 82/18 mixture of 3-acetylcyclohexene and 2-chlorocyclohexyl methyl ketone in 89% combined yield.

The following Lewis acids are also claimed to be superior to $AlCl_3$: $Zn(Cu)/CH_2I_2$ (AcCl, CH_2Cl_2, Δ), by which cyclohexene is converted into acetylcyclohexene in 68% yield (after treatment with KOH/MeOH);[58] $ZnCl_2$ (AcCl, Et_2O/CH_2Cl_2, −75 °C → −20 °C), by which 2-methyl-2-butene is converted into a 15:85 mixture of 3,4-dimethyl-4-penten-2-one and 4-chloro-3,4-dimethyl-2-pentanone in 'quantitative' combined yield;[59] and $SnCl_4$, by which cyclohexene (AcCl, CS_2, −5 °C → rt) is converted into acetylcyclohexene in 50% yield (after dehydrochlorination with $PhNEt_2$ at 180 °C),[60] methylcyclohexene (CS_2, rt) is converted into 1-acetyl-2-methylcyclohexene in 48% yield (after dehydrochlorination),[52] and camphene is converted into an acetylated derivative in ∼65% yield.[49c]

Conducting the acetylation in the presence of a nonnucleophilic base or polar solvent is reported to be advantageous. For example, methylenecyclohexane can be converted into 1-cyclohexenylacetone in 73% yield by treatment with $AcSbCl_6$ in the presence of Cy_2NEt (CH_2Cl_2, −50 °C → −25 °C, 1 h)[61] and cyclohexene can be converted into 3-acetylcyclohexene in 80% yield by treatment with $AcBF_4$ in $MeNO_2$ at −25 °C.[62]

Employment of Ac_2O instead of AcCl is also advantageous in some cases. For example, methylcyclohexene can be converted into 3-acetyl-2-methylcyclohexene in 90% yield by treatment with $ZnCl_2$ (neat Ac_2O, rt, 12 h).[63]

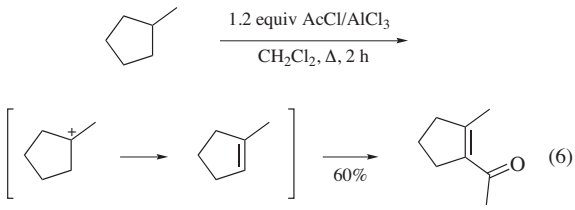
Finally, alkenes can be diacetylated to afford pyrylium salts by treatment with excess $AcCl/AlCl_3$,[55b,56,64] albeit in low yield (eq 5).[64a]



(5)

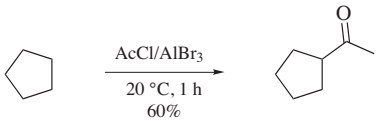
Acetylation of Alkynes. Under Friedel–Crafts conditions ($AcCl/AlCl_3$, CCl_4, 0–5 °C), acetylene undergoes acetylation to afford β-chlorovinyl methyl ketone in 62% yield[4] and under similar conditions ($AcSbF_6$, $MeNO_2$, −25 °C) 5-decyne undergoes acetylation to afford 6-acetyl-5-decanone in 73% yield.[65]

Acetylation of Saturated Alkanes. Saturated alkanes, on treatment with a slight excess of $AcCl/AlCl_3$ at elevated temperature, undergo dehydrogenation (by hydride abstraction followed by deprotonation) to alkenes, which undergo acetylation to afford vinyl methyl ketones. The hydride-abstracting species is believed to be either the acetyl cation[66] or $HAlCl_4$,[67] with most evidence favoring the former. Perhaps because the alkenes are generated slowly and consumed rapidly, and therefore are never present in high enough concentration to dimerize, yields are typically higher than those of acetylation of the corresponding alkenes.[53b,68] A similar hypothesis has been offered to explain the phenomenon that the yield from acetylation of tertiary alkyl chlorides is typically higher than the yield from acetylation of the corresponding alkenes.[55b,64a] For example, methylcyclopentane on treatment with $AcCl/AlCl_3$ (CH_2Cl_2, Δ) undergoes acetylation to afford 1-acetyl-2-methylcyclopentene in an impressive 60% yield (eq 6).[53b,66a]



(6)

If the reaction is carried out with excess alkane, a second hydride transfer occurs, resulting in reduction of the enone to the corresponding saturated alkyl methyl ketone.[69,70] For example, stirring $AcCl/AlCl_3$ in excess cyclohexane (30–35 °C, 2.5 h) affords 2-methyl-1-acetylcyclopentane in 50% yield (unpurified; based on AcCl)[55a,69,71] and stirring $AcCl/AlBr_3$ in excess cyclopentane (20 °C, 1 h) affords cyclopentyl methyl ketone in 60% yield (based on AcCl; eq 7).[55c]



(7)

If the reaction is carried out with a substoichiometric amount of alkane, the product is either a 2:1 adduct (if cyclic)[53b,66a] or pyrylium salt (if acyclic).[66b,68b]

Unbranched alkanes also undergo acetylation, but at higher temperature, so yields are generally lower. For example, acetylation of cyclohexane by $AcCl/AlCl_3$ requires refluxing in $CHCl_3$ and affords 1-acetyl-2-methylcyclopentene in only 36% yield.[55c,72]

Despite the modest to low yields, acetylation of alkanes provides a practical method for accessing simple methyl ketones because all the input raw materials are cheap.

Coupling with Organometallic Reagents. Coupling of organometallic reagents with AcCl is a valuable method for preparation of methyl ketones. Generally a catalyst (either a Lewis acid or transition metal salt) is required.

Due to the large number and varied characteristics of the organometallics, comprehensive coverage of the subject would require discussion of each organometallic reagent individually, which is far beyond the scope of this article. Information pertaining to catalyst and condition selection should therefore be accessed from the original literature; some seminal references are given in Table 1.

***C*-Acetylation of Enolates and Enolate Equivalents.** β-Diketones can be synthesized by treatment of metal enolates with AcCl. *O*-Acetylation is often a significant side reaction, but the amount can be minimized by choosing a counterion that is bonded covalently to the enolate[6] such as copper[132] or zinc,[133] and by using AcCl rather than Ac_2O.[6a] Proton transfer from the product β-diketone to the starting enolate is another common side reaction.[134] Alternative procedures for effecting *C*-acetylation that avoid or minimize these side reactions include Lewis acid-catalyzed acetylation of the trimethylsilyl enol ether derivative (AcCl/cat. $ZnCl_2$, CH_2Cl_2 or CH_2Cl_2/Et_2O, rt)[135] and addition of ketene to the morpholine enamine ($AcCl/Et_3N$, $CHCl_3$, rt).[136]