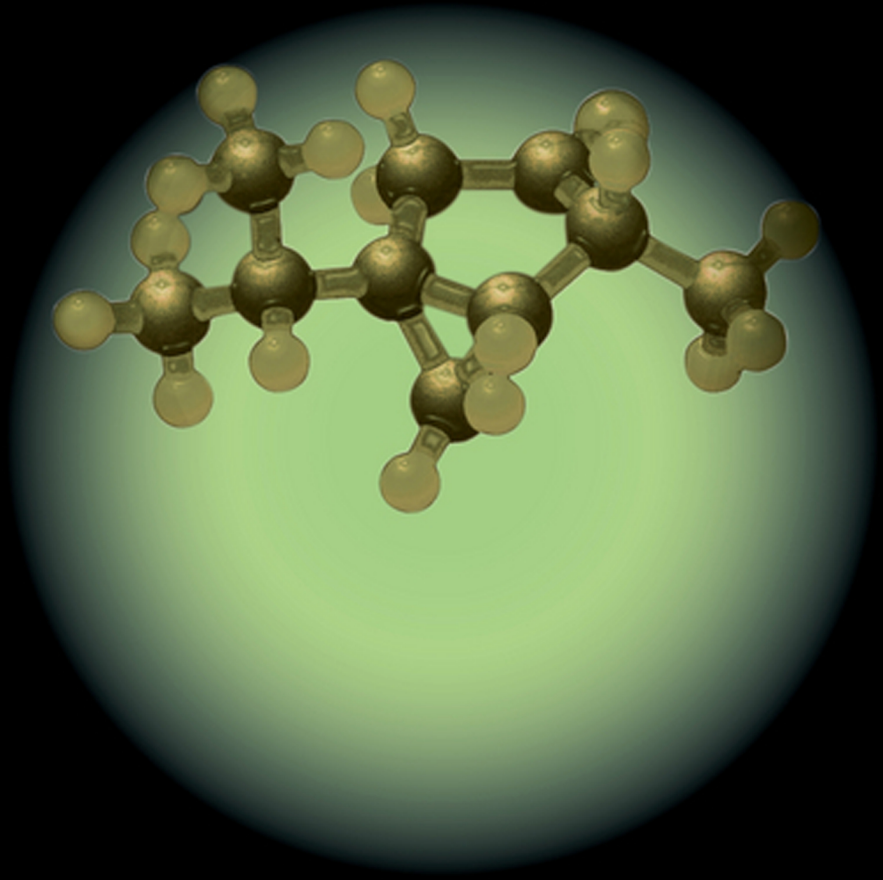

Handbook of Reagents for Organic Synthesis

Reagents for Heteroarene Synthesis

Edited by

André B. Charette

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e-EROS Editorial Board

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Preface

The eight-volume *Encyclopedia of Reagents for Organic Synthesis (EROS)*, authored and edited by experts in the field, first published in 1995, provided mini-reviews describing the properties and reactions of approximately 3000 reagents. In 2002, the entire *EROS* collection with updates and additions was made available on the Internet under the acronym *e-EROS*. The second edition of the encyclopedia, *EROS-II*, was published in March 2009 containing the entire collection of reagents—4111 at the time of publication in a 14-volume set. While the comprehensive nature of *EROS-II* and the dynamic expansion of *e-EROS* render them invaluable as reference works, their very size limits their practicability in a laboratory environment. For this reason, a series of sharply targeted and inexpensive one-volume *Handbooks of Reagents for Organic Synthesis (HROS)* was introduced by the original editors of EROS in 1999:

Reagents, Auxiliaries and Catalysts for C–C Bond Formation
Edited by Robert M. Coates and Scott E. Denmark

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

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Activating Agents and Protecting Groups
Edited by Anthony J. Pearson and William R. Roush

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

Chiral Reagents for Asymmetric Synthesis
Edited by Leo A. Paquette

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André Charette, a member of the e-EROS Editorial Board, now presents the 17th volume in the HROS series with a companion to his recent heteroarene functionalization work entitled *Reagents for Heteroarene Synthesis.*

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Introduction

The synthetic power to create simple and elaborated heteroarene scaffolds has played a predominant role in driving natural product synthesis, pharmaceutical and agrochemical development, and materials science. Although many simple unsubstituted heteroarenes were first isolated from natural sources, most heteroaromatics are not naturally abundant and, therefore, effective synthetic tools are required to navigate heteroarene synthesis. As an example, pyridine can be isolated from coal tar; however, it can be more efficiently prepared on an industrial scale via the Chichibabin or other related name reactions. One can only think of all the synthetic processes that have been developed in the 1800s that have given rise to name reactions. For the last two centuries, chemists have devoted their efforts toward constructing diverse and powerful synthetic strategies to assemble heteroarenes. The vast library of name reactions targeting heteroaromatic synthesis is a testament to these laborious and heroic endeavors. For example, the Paal-Knorr pyrrole synthesis, the Fischer indole synthesis, the Hantzsch pyridine synthesis, and the Bischler–Napieralski isoquinoline synthesis represent only a few of the fundamental classical textbook reactions. In many instances, these methods involve cyclodehydration processes employing simple and versatile building blocks.

Despite the notable contributions to the heteroarene synthetic toolbox, many of these classical protocols necessitate harsh conditions and/or toxic and hazardous reagents. With the advent of transition metal catalysis, heteroarene synthesis has evolved to include catalytic, atom economical, and more sustainable reaction conditions, providing access to both well-established and novel heteroarenes. Such transition-metal-mediated strategies have forged innovative synthetic disconnections, have expanded the range of possible heteroarene precursors, and have improved functional group tolerance. At present, novel methodologies allow not only the production of known heteroarenes but also the specific incorporation of heteroatoms at their desired positions within novel structural cores.

The pharmaceutical industry continues to exploit the varied and unique properties present in the heteroaromatic spectrum toward designing new drug candidates. It is of no surprise that 60% of the 100 top-selling small-molecule drugs contain heteroarenes. Within US FDA approved drugs, pyridine is the second most frequently used nitrogen heterocycle, whereas thiazole and imidazole rank sixth and seventh, respectively. These striking statistics emphasize strong academic and industrial motivations to cultivate new, improved, cost-effective, and robust heteroaromatic synthetic reagents.

Nature has successfully integrated the heteroarene moiety within several highly complex heteroaryl-based natural products. For example, the important porphyrin motif has stimulated the advancement of synthetic methods to furnish highly substituted pyrroles of increasing complexity. Additionally, the indole core is prominently located in important indole alkaloids such as lysergic acid, vincristine, and cathenamine. In the last few decades, several de novo chemoselective heteroarene syntheses have been discovered and implemented to allow full control over substituent positions during heteroarene assembly. Finally, heteroarenes formulate integral parts of important ligand classes such as the pybox family, the *N*-heterocyclic carbene ligands, many chiral bis(heteroarylphosphine) ligands, and substituted phenanthrolines.

This handbook on heteroarene synthesis serves as a companion to the previous handbook, *Reagents for Heteroarene Functionalization*. Both handbooks are complementary and provide an extensive overview of the reagents currently available for heteroarene synthesis.

Given the structural diversity of both the heteroarenes and the synthetic reagents required, in addition to the magnitude and diversity of synthetic precursors, only representative reagents could be provided in the handbook.

As an example, a multicomponent preparation of pyridine using the Hantzsch reaction could easily involve up to three or four small building blocks (e.g., aldehyde, two ketoester units, ammonia source) that could be modified at will.

This handbook contains 57 new reagents and 42 updated reagents.

As an additional resource to the reader for finding relevant information, a listing of Recent Reviews and Monographs follows this section that are grouped by the type of heteroarenes.

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Recent Review Articles and Monographs

Recent Reviews

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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 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 ensure 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: www.wileyonlinelibrary.com/ref/eros and click on the InChI and InChIKey link.

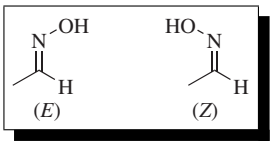
General Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
BBN	borabicyclo[3.3.1]nonane
BCME	bis(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

A

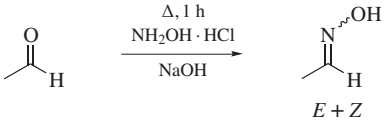
Acetaldoxime



[107-29-9] C_2H_5NO (MW 59.07)
InChI = 1/C2H5NO/c1-2-3-4/h2,4H,1H3
InChIKey = FZENGILVLUJGJX-UHFFFAOYAK
(*E*)
[5780-37-0]
InChI = 1/C2H5NO/c1-2-3-4/h2,4H,1H3/b3-2+
InChIKey = FZENGILVLUJGJX-NSCUHMNNBP
(*Z*)
[5775-72-4]
InChI = 1/C2H5NO/c1-2-3-4/h2,4H,1H3/b3-2-
InChIKey = FZENGILVLUJGJX-IHWYPQMZBM

(acetaldehyde equivalent; acetylation of arenes via diazonium salts;[1] synthesis of aldoximes;[2] rearrangement into acetamide;[3,4] synthesis of heterocycles, e.g. 2-isoxazolines,[5] imidazoles;[6] thiazolidines;[7] precursor for acetonitrile oxide, a useful 1,3-dipole for cycloadditions;[8] 1,3-dipolar cycloaddition[5,9,10])

Alternate Name: acetaldehyde oxime.
Physical Data: (*E*) and (*Z*) mixture bp 114–115°C; mp 47°C.
Solubility: sol most organic solvents, e.g. THF, $CHCl_3$, benzene, xylene, diethyl ether, 1,2-dichloroethane.
Form Supplied in: widely available commercially. Commercial samples, which had been refrigerated for several months, showed (*Z*):(*E*) ratios of 10–20:1.[2]
Analysis of Reagent Purity: ^{1}H NMR.
Preparative Methods: reaction of freshly distilled ***Acetaldehyde*** with ***Hydroxylamine*** hydrochloride in the presence of a base (eq 1).[3,11]



(1)

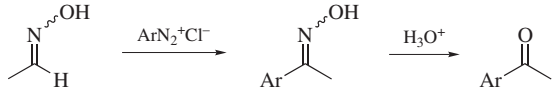
Handling, Storage, and Precautions: the oxime is preferably freshly prepared. The freshly prepared solid compound decomposes slowly on standing. Use in a fume hood.

Original Commentary

Norbert De Kimpe
University of Ghent, Ghent, Belgium

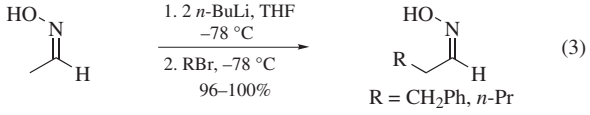
Introduction. Unsymmetrical oximes, like acetaldoxime, occur as a mixture of (*E*) and (*Z*) isomers across the carbon–nitrogen double bond (often referred to as *syn* and *anti* isomers, respectively). The position of the equilibrium changes with the conditions. A frequently reported equilibrium is situated around 40% (*E*) in the pure state and 46% (*E*) in aqueous acid,[12] but the position of the equilibrium is independent of the temperature and the concentration of the acid.[13] (*Z*)-Acetaldoxime can be prepared by slow crystallization of a freshly distilled mixture of (*E*)/(*Z*) isomers. ^{13}H NMR[11,14] and ^{13}C NMR[15] have been used to establish the (*E*)/(*Z*) configurations of oximes.

Acetylation of Arenes via Diazonium Salts. The reaction of acetaldoxime with aromatic diazonium salts affords oximes of acetophenones, which are hydrolyzed in acid medium to give aryl methyl ketones (eq 2).[1]

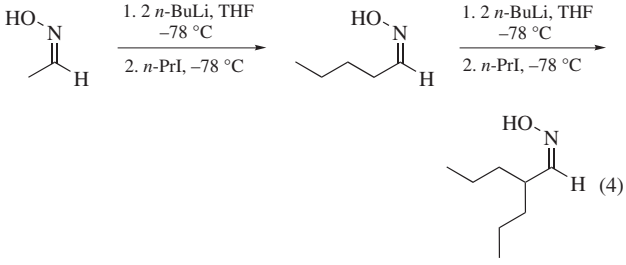


(2)

α-Alkylation of Acetaldoxime. Deprotonation of acetaldoxime with 2 equiv of ***n-Butyllithium*** at −78 °C generates the dianion which reacts with ***Benzyl Bromide*** or 1-iodopropane to give excellent yields of α-alkylated (*Z*)-oximes (eqs 3 and 4).[2] α,α-Dialkylation by further alkylation in similar way has been achieved (eq 4).[2] It is generally known that ketone oximes can be deprotonated and alkylated regiospecifically *syn* to the oxime hydroxy group.[16,17] It is essential to perform the deprotonation and alkylation at −78 °C as otherwise no α-alkylated oximes are isolated, the major byproducts being nitriles.[16]

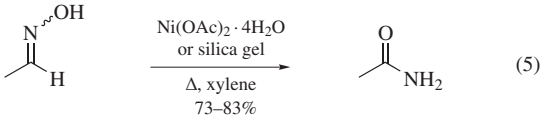


(3)



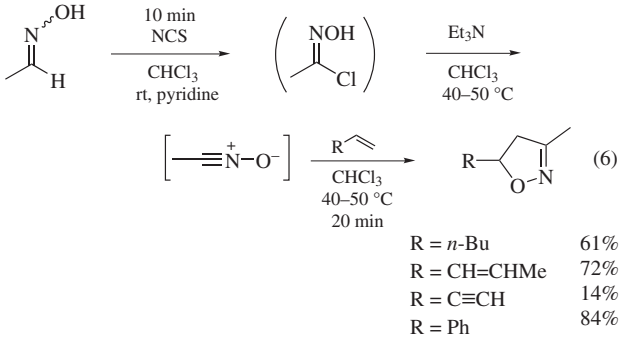
(4)

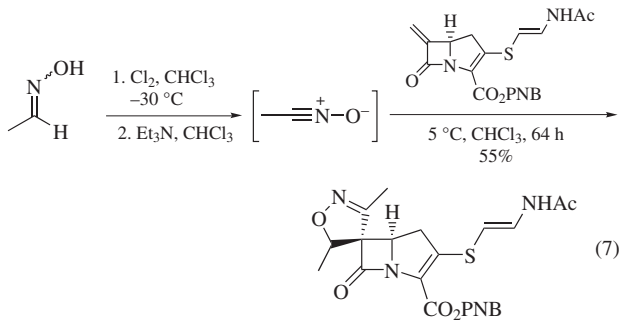
Rearrangement into Acetamide. Heating of acetaldoxime in xylene in the presence of 0.2 mol % ***Nickel(II) Acetate***[3] or silica gel[4] as catalyst caused isomerization into acetamide (eq 5).



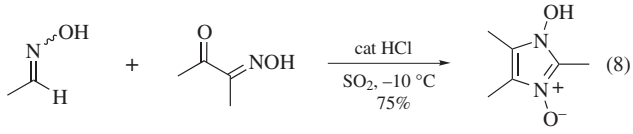
(5)

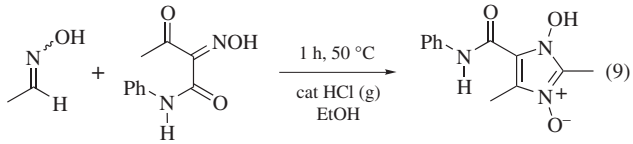
Synthesis of Heterocycles. Chlorination of acetaldoxime with ***N-Chlorosuccinimide***[5] or ***Chlorine*** gas[8,18] in chloroform affords acetohydroxamic acid chloride, which suffers dehydrochlorination with ***Triethylamine*** to give ***Acetonitrile N-Oxide***. The latter 1,3-dipole undergoes 1,3-dipolar cycloaddition to alkenes giving 2-isoxazolines in a one-pot procedure (eq 6).[5] This reaction is also suitable for the construction of more complex molecules such as the conversion of a 6-ethylideneolivanic acid derivative into the corresponding spiroisoxazoline (eq 7).[8]



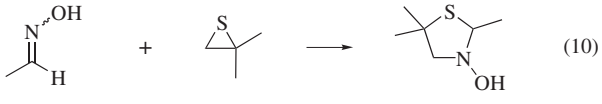


The cyclocondensation of acetaldoxime with biacetyl monooxime yields 1-hydroxy-2,4,5-trimethylimidazole 3-oxide,[19] originally believed to be 4-hydroxy-3,4,6-trimethyl-1,2,5-oxadiazine.[20] The reaction is preferably performed in liquid sulfur dioxide in the presence of catalytic amounts of hydrogen chloride (eq 8),[6] and works as well with other α-oximino ketones (eq 9).[21]

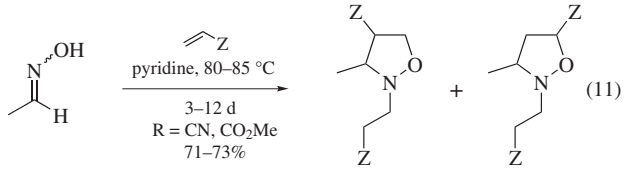


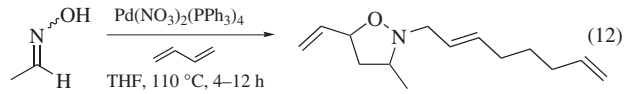


Upon reaction of acetaldehyde oxime with 2,2-dimethylthiirane, ring expansion to 3-hydroxy-2,5,5-trimethylthiazolidine occurs (eq 10).[7]

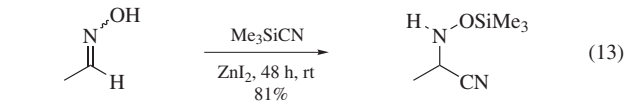


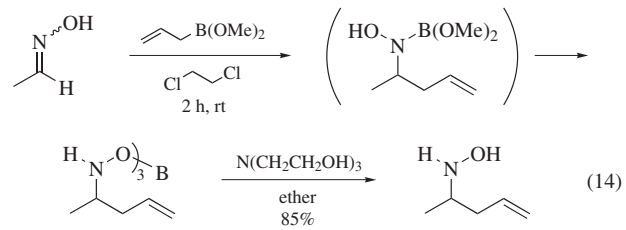
1,3-Dipolar Cycloaddition. Acetaldoxime cycloadds very slowly to ***Methyl Acrylate*** and ***Acrylonitrile***, giving 2:1 adducts as mixtures of regioisomers and stereoisomers (eq 11).[10] The palladium-catalyzed cycloaddition of the reagent to 1,3-butadiene yields an isoxazolidine via the intermediacy of a nitrone which undergoes 1,3-dipolar cycloaddition (eq 12).[9]



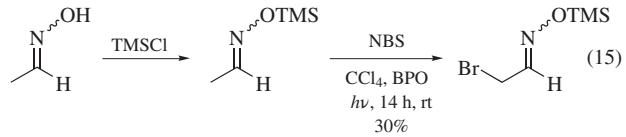


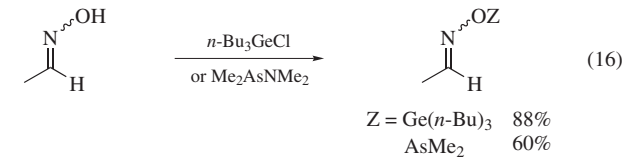
Addition Reactions Across the Carbon–Nitrogen Double Bond. ***Cyanotrimethylsilane*** adds to acetaldoxime to give the cyanated adduct (eq 13),[22] while allylboronates behave similarly to afford the adduct, which disproportionates and can subsequently be cleaved to the alkenic hydroxylamine (eq 14).[23]

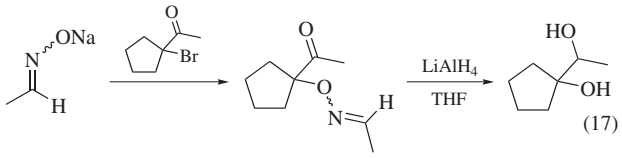




O*-Functionalization.** α-Bromo aldoximes are difficult to obtain. Direct α-bromination of aldoximes with a variety of brominating agents was not successful, but smooth bromination of the *O*-silylated derivative was accomplished (eq 15).[24] Functionalization at the oxygen atom has been accomplished with organogermanium[25] and organoarsenium[26] reagents (eq 16), while *O*-alkylation has been performed with the sodium salt of acetaldoxime and an α-bromo ketone.[27] ***Lithium Aluminum Hydride readily effected hydrogenolysis of the N–O bond to afford the corresponding 1,2-diol (eq 17).[27]

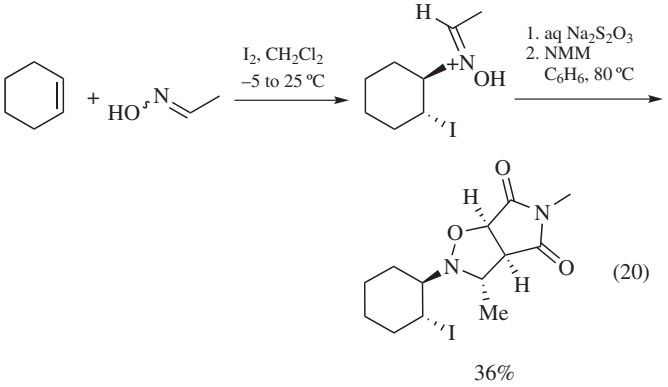






(17)

Miscellaneous. Thermal decomposition of alkyl peresters or peroxides in H-donor solvents, e.g. cycloalkanes or ethers, in the presence of acetaldoxime afforded C-1 alkylated products.[28] The reaction involves carbon radical addition to the carbon–nitrogen double bond.



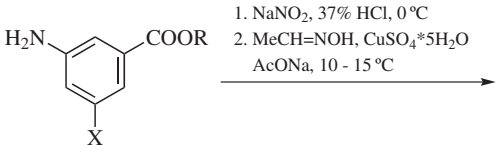
(20)

36%

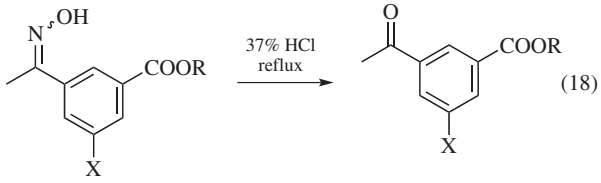
First Update

Andrey Platonov & George Nikonov
Gainesville, FL, USA

Acetylation of Arenes via Diazonium Salts. A diazotization/acylation sequence was used to furnish acetyl derivatives of aromatic acids (eq 18).[29]



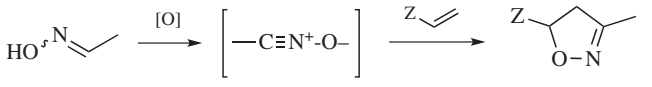
R = Me, Et; X = NO_2, COOMe



(18)

42%

1.3-Dipolar Cycloaddition. The reactions of 1,3-dipolar cycloaddition of nitrile oxide generated from acetaldoxime with diverse alkenes result in the formation of 3-methyl-2-isoxazoline derivatives (eq 19).[30,31]



35–93%

[O] = NCS, Oxone

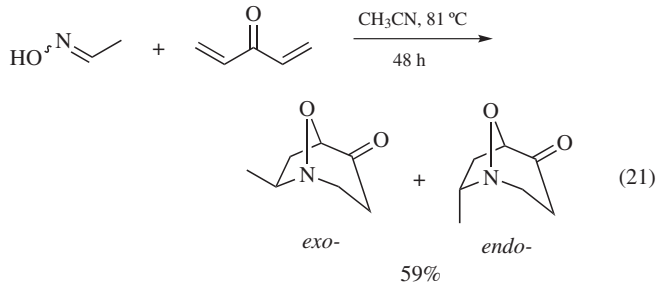
(19)

Z = Ph; residue of 17-hydroxy-steroids (estrone series)

Cascade reactions of oxime – nitrone – cycloaddition were developed.[32] Nucleophilic addition of acetaldehyde oxime to cyclohexene in the presence of iodine affords intermediate salt as a single stereoisomer (eq 20).

The free base derived from the salt undergoes 1,3-dipolar cycloaddition with *N*-methylmaleinimide (NMM) to give substituted dihydro-2*H*-pyrrolo[3,4-*d*]isoxazole as a single stereoisomer in 36% overall yield.

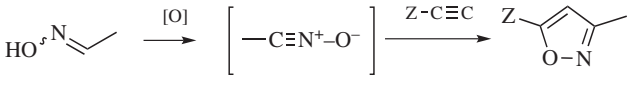
The tandem 1,3-azaprotio cyclotransfer–cycloaddition reaction between acetaldoxime and divinyl ketone affords a mixture of *exo*- and *endo*-isomers (3.4:1) of 7-methyl-1-aza-8-oxabicyclo[3.2.1]octan-4-ones (eq 21).[33]



(21)

59%

The synthesis of 5-substituted 3-methylisoxazoles is possible from acetaldoxime and terminal acetylenic compounds (eq 22). The latter include propargyl chloride,[34] propargyl alcohols,[35–37] propargyl carbamates,[38] tributylstannylacetylene,[39] and 5-ethynyl-2′-deoxyuridines.[40]



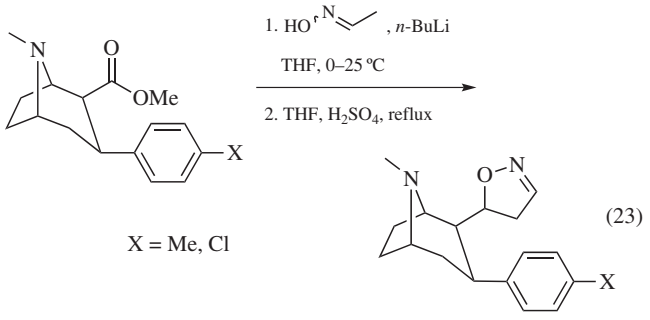
46–94%

[O] = NCS, Chloramine B, NaOCl

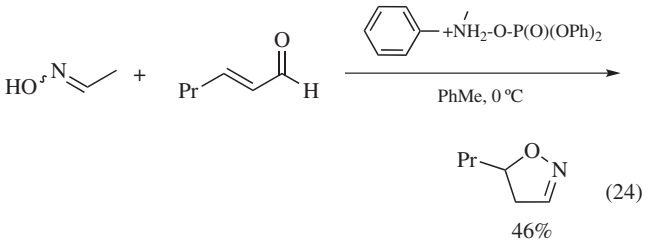
(22)

Z = C(X)Alk$_n$Ph$_m$(X = Cl, OH, ArNHCOO;
n = 0-2; *m* = 0, 1);
2′-deoxyuridin-5-yl;
residue of 20-hydroxysteroids;
SnBu3

Synthesis of Heterocycles. Acetaldoxime was used to synthesize 3β-(substituted phenyl)-2β-isoxazol-5-yl-tropanes[41] (eq 23) and 5-propyl-4,5-dihydroisoxazole from the aliphatic α,β-unsaturated aldehyde in the presence of an anilinium salt catalyst (eq 24).[42]

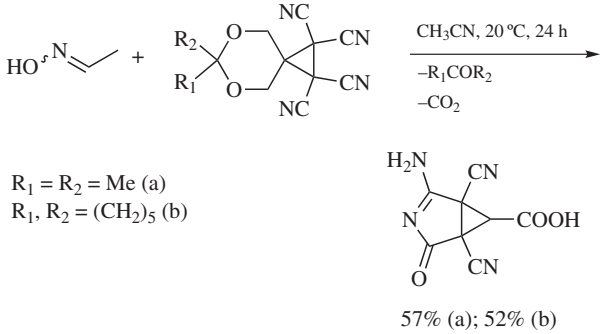


(23)



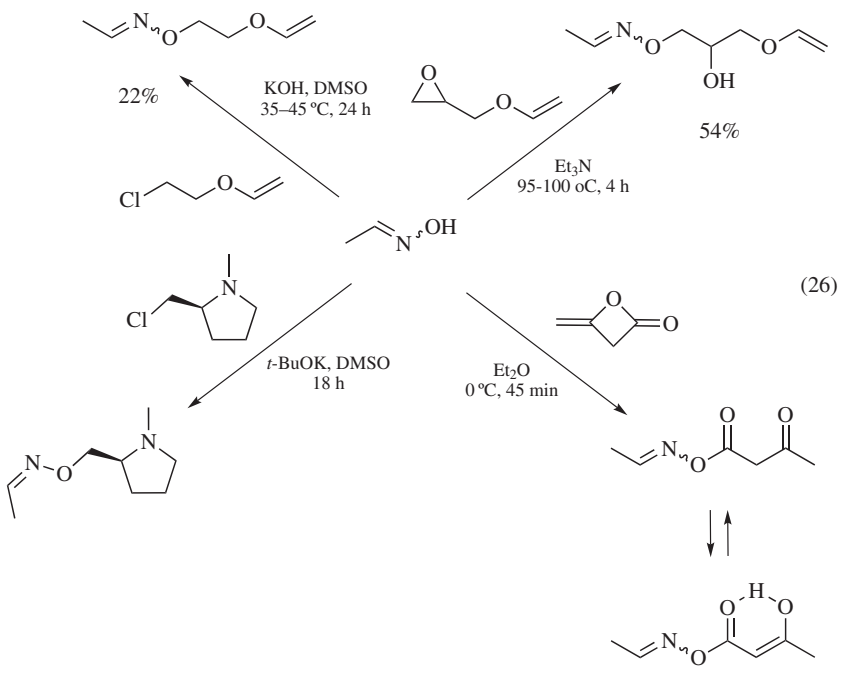
(24)

The reactions of tetracyanospirocyclopropane derivatives with acetaldehyde oxime give 2-amino-4-oxo-1,5-dicyano-3-azabicyclo[3.1.0]hex-2-ene-6-carboxylic acid (eq 25).[43]



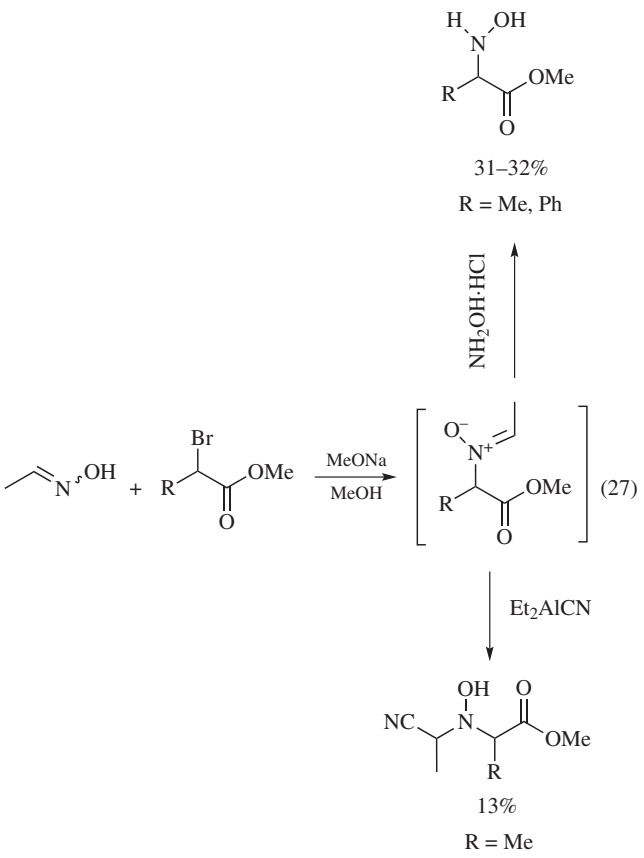
(25)

Functionalization. O-Functionalization of acetaldoxime was performed by 2-chloroethyl vinyl ether,[44] (2*S*)-*N*-methyl-2-chloromethylpyrrolidine,[45] vinyl glycidyl ether,[46] and 4-methylene-oxetan-2-one[47] (eq 26).

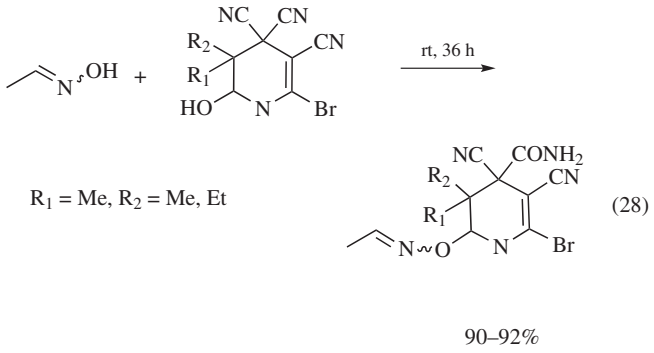


(26)

N-Alkylation of acetaldoxime with the formation of nitrone was used in the synthesis of *N*-hydroxy- and *N*-α-cyanoethylamino acid methyl esters via the so-called 'acetaldoxime route' (eq 27).[48]

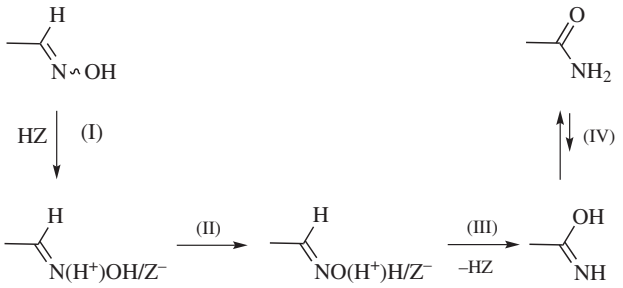


The authors[49] stated that in reactions of 5,5-dialkyl-2-bromo-6-hydroxy-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles with acetaldehyde oxime, the electrophilic carbon atom in the axial cyano group on C4 favors the replacement of the hydroxy group according to a 'push-pull' mechanism resulting in conversion of the cyano group into a carbamoyl moiety (eq 28). The reactions occur under mild conditions, and no catalyst was necessary; either anhydrous acetaldehyde oxime or anhydrous acetonitrile can be used as solvent.



The direct chlorination of acetaldehyde oxime using equimolar *N*-chlorosuccinimide in DMF at 20–25°C afforded acetohydroximinoyl chloride.[50]

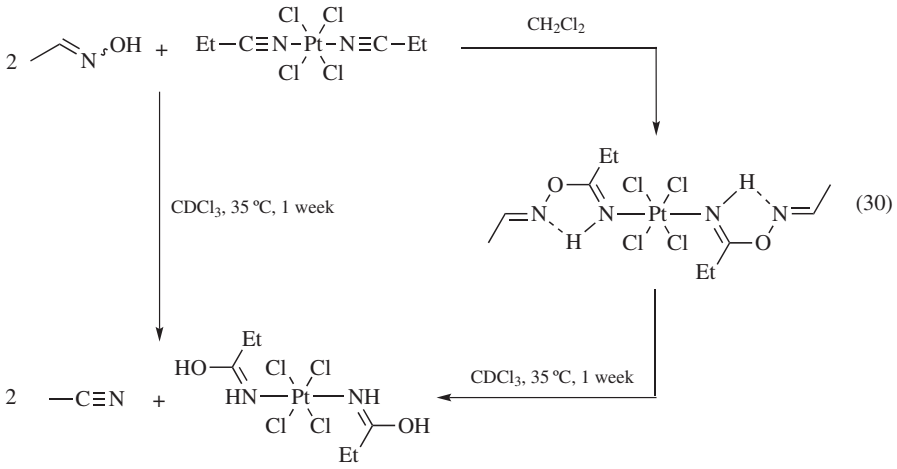
Rearrangement to Acetamide. The mechanism of Beckmann rearrangement of (*Z*)- and(*E*)-acetaldoxime catalyzed by the Faujasite zeolite was investigated by both the quantum cluster and embedded cluster approaches at the B3LYP level of theory (eq 29).[51]



HZ = Brønsted acid site of zeolite

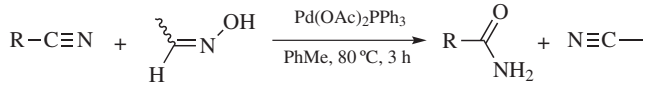
For the (*Z*)-acetaldehyde oxime, the rate-limiting step is the 1,2 H-shift step II while the rate-limiting step of (*E*)-acetaldehyde oxime could be either the 1,2 H-shift step or the rearrangement step III.

Transformations to Acetonitrile and Acetaldehyde. Acetaldoxime reacts with complex *trans*-[$PtCl_4(EtCN)_2$] to afford products of the addition of the aldoxime group across the CN triple bond (eq 30).[52]



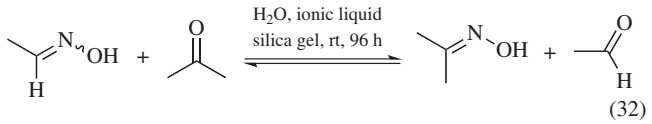
In $CDCl_3$ solution, the imino complex undergoes the spontaneous imine ligand dissociation to afford the carboxamide complex *trans*-$[PtCl_4\{NH{=}C(Et)OH\}_2]$ and acetonitrile, thus providing the first example of a ligand-mediated dehydration of aldoximes.

An efficient palladium-catalyzed protocol for the hydration of nitriles to amides with acetaldoxime has been developed (eq 31).[53] Acetaldoxime serves as an efficient water surrogate that delivers water to the substrate nitrile.



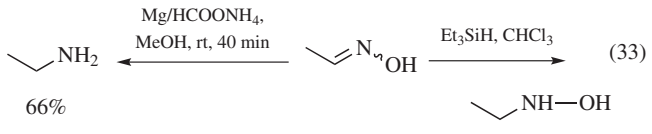
R = Ph, *p*-CNC_6H_4, *o*-FC_6H_4, 2,6-di-ClC_6H_3, *p*-MeO-C_6H_4, *p*-MeC_6H_4, Ph-CH=C(Ph), vinyl, Br, phenethyl, $PhC(O)CH_2$ 76–93% (31)

An equilibrium oxime–carbonyl transformation in silica gel-supported ionic liquid catalysts and water media was reported (eq 32).[54,55]



(32)

Reduction. Earlier reports reveal that catalytic transfer hydrogenation of oximes to amines had been achieved with systems such as ammonium formate/10% Pd/C[56] and cyclohexene/10% Pd/C.[57] But these systems require reaction times as long as 5–10 hours at reflux and expensive catalyst, and only afford low yields. Authors of the current work[58] reported a rapid, selective and simple reduction of acetaldoxime to ethylamine by using low cost magnesium powder and ammonium formate at room temperature (eq 33). The first example of reduction of acetaldoxime with triethylsilane into the ethylhydroxylamine was described[59] (eq 33).



(33)

Miscellaneous. Acid-promoted (*E*)/(*Z*)-isomerization of oximes in water was studied by means of theoretical calculations at the B3LYP/6-31G(d,p) level of a simple derivative, acetaldoxime.[60] Authors have shown that (*E*)/(*Z*)-isomerization of acetaldoxime in aqueous solution should preferentially proceed by rotation around the oxime C–N bond with a concerted formation of a C(oxime) – O(water) bond that strongly stabilizes the system.

The results of experimental studies and ab initio calculations of the (*Z*)-CH_3CH=N-OH and (*E*)-CH_3CH=N-OH complexes with N_2 are presented.[61] Authors have noticed that the (*Z*)-acetaldoxime isomer shows stronger bonding ability to nitrogen than the (*E*)-isomer, which suggests that the O–H group of (*Z*)-isomer is more acidic than that of (*E*)-isomer.

Related Reagents. Acetaldehyde; Acetaldehyde *N*-*t*-Butylimine; Acetonitrile *N*-Oxide; Formaldoxime; Hydroxylamine; cyclohexene; n-methylmaleinimide; divinyl ketone; propargyl chloride; propargyl alcohols; propargyl carbamate; tributylstannylacetylene; 2-chloroethyl vinyl ether; vinyl glycidyl ether; 4-methylene-oxetan-2-one; acetonitrile.

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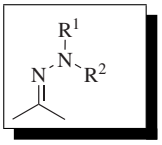
Acetone Hydrazone[1]



(**1**; $R^1 = R^2 = H$)
[5281-20-9] $C_3H_8N_2$ (MW 72.11)
InChI = 1/C3H8N2/c1-3(2)5-4/h4H2,1-2H3
InChIKey = JIQXKYSNGXUDJU-UHFFFAOYAV
(**2**; $R^1 = H$, $R^2 = Ph$)
[103-02-6] $C_9H_{12}N_2$ (MW 148.21)
InChI = 1/C9H12N2/c1-8(2)10-11-9-6-4-3-5-7-9/h3-7,11H, 1-2H3
InChIKey = JQLKSEQEILIJEG-UHFFFAOYAR
(**3**; $R^1 = R^2 = Me$)
[13483-31-3] $C_5H_{12}N_2$ (MW 100.17)
InChI = 1/C5H12N2/c1-5(2)6-7(3)4/h1-4H3
InChIKey = IDSMDKUVIBSETN-UHFFFAOYAD

(metalated dimethylhydrazones as anion equivalents are especially useful for regioselective alkylations[1,2] and as precursors of unsymmetrical ketone hydrazones;[1,3] *gem*-dimethyl synthons in cycloaddition reactions[4])

Physical Data: (**1**) n_D^{22} 1.4607, colorless liquid, bp 124–125 °C; (**2**) mp 42 °C, rhombic crystals, bp 163 °C/50 mm Hg; (**3**) light yellow liquid, bp 94–95.5 °C (92–94 °C[5]).

Solubility: sol alcohol, ether, THF, CH_2Cl_2.

Analysis of Reagent Purity: (**1**) nitrogen evolution upon treatment with glacial acetic acid; acetone azine is a common impurity; (**2**, **3**) IR or NMR spectroscopy.

Preparative Methods: (**1**) is best prepared by either of two methods: from the acetone azine[7] or by an exchange reaction between ***Hydrazine*** and (**3**) in the presence of glacial acetic acid.[6,8] Both methods give nearly quantitative yields of (**1**), but the latter method produces hydrazone without azine contamination. The general method for the preparation of phenylhydrazones can be applied to the synthesis of (**2**).[1a,9] Equimolar amounts of ***Acetone*** and ***Phenylhydrazine*** are refluxed gently in aqueous ethanol with catalytic amounts of glacial acetic acid. The phenylhydrazone separates out upon cooling and can be recrystallized from aqueous ethanol. The synthesis of (**2**) by reaction of acetone, ammonia, and aniline in the presence of water has also been reported.[9b] The dimethylhydrazone can be prepared in very high yield by a general procedure for ketones using anhydrous ***N,N-Dimethylhydrazine***.[6,8] Hydrazines should be handled with care because of their toxicity. *Caution*! Anhydrous hydrazine is also highly reactive with oxidizing agents; the syntheses should be carried out behind a protective screen, in a fume hood.

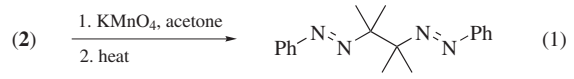
Handling, Storage, and Precautions: (**1**) usually prepared just before use; unstable in the pure liquid state; disproportionates slowly to hydrazine and acetone azine at rt. Use in a fume hood. It is claimed that simple hydrazones can be stored indefinitely with minimal deterioration in the absence of moisture in the solid state at low temperature.[6] Azine formation is rapid in the

presence of moisture. Regeneration of old samples is accomplished by heating the hydrazone at 100 °C for 12–16 h before distillation.[7] Hydrazones (**2**) and (**3**) are relatively stable and can be stored for long periods of time without deterioration.

Hydrazone Oxidations. The reactions of ketone hydrazones depend largely on the degree and kind of substitution on the *N*-amino group. Hydrazone (**1**) ($R^1 = R^2 = H$) is most prone to oxidation. Oxidation of (**1**) in the presence of ***Mercury(II) Oxide*** or ***Silver(I) Oxide*** and KOH serves as the easiest route to ***2-Diazopropane***.[10] The latter undergoes 1,3-cycloaddition reactions with electrophilic C=C bonds to form substituted pyrazoles,[11] vinylic and epoxy quinones,[12] and pyrazolines.[13] With ***Diphenylacetylene*** a pyrazole is formed that can be subsequently photolyzed to a conjugated alkynylcyclopropane.[14] Thus (**1**), being a precursor of 2-diazopropane, serves as a potential source of *gem*-dimethyl groups in cycloaddition reactions.

Oxidative denitrogenation has also been accomplished by a variety of electrophilic reagents. With HgO/***Mercury(II) Acetate***, (**1**) forms an acetoxy adduct that yields 4-acetoxy-4-methylvaleronitrile upon reaction with ***Acrylonitrile***.[15] In general, simple ketone hydrazones react with excess ***Benzeneselenenyl Bromide*** in the presence of a hindered guanidine base to afford phenyl vinyl selenide[16] or with excess ***Iodine*** in triethylamine–THF to afford vinyl iodides.[17] 1-Alkenyl cobalt complexes are formed in the presence of a Co–dioxygen complex. Subsequent reduction by ***Sodium Borohydride*** produces propene from (**1**) and *cis* alkenes from higher aliphatic ketone hydrazones.[18]

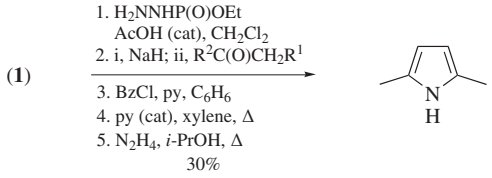
Phenylhydrazone (**2**) couples to form a C–N dimer as the oxidation product when treated with ***Potassium Permanganate*** in acetone. Upon heating, the dimer gives a vicinal bis(azo)alkane (eq 2).[19]



(1)

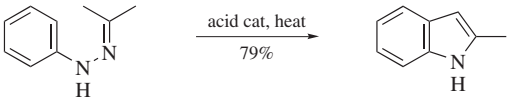
Oxidation of (**3**) generally leads to C=N bond cleavage and has been utilized most successfully to regenerate acetone and other ketones from their dialkylhydrazones. Oxidizing agents that are commonly used for this purpose include ***Ozone*** at low temperature,[20a] ***Sodium Perborate***, ***Sodium Periodate***, and H_5IO_6.[20] With ***Selenium(IV) Oxide***, however, oxidation leads to α-carbonylation in high yield.[21]

Heterocycles. 1,3-Dipolar cycloaddition reactions involving hydrazones offer a very versatile means of synthesizing five-membered heterocyclic rings. Cycloadditions between (**1**) and nitrile oxides form oxadiazolines in modest yields.[22] Cyclocondensation of benzoylhydrazinoacrylate from (**1**) affords aminoquinolonecarboxylates.[23] An alternative to the Piloty–Robinson pyrrole synthesis has been used by Baldwin[24] to prepare pyrroles from any enolizable aldehyde or ketone via azines synthesized from the corresponding hydrazones. The reaction is shown for (**1**) (eq 2).

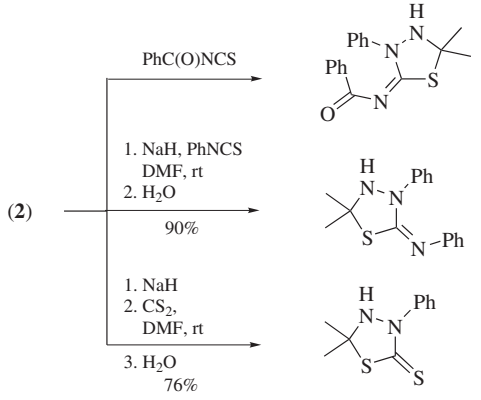


(2)

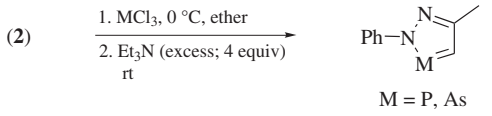
The Fischer indole synthesis provides an efficient route for the synthesis of indoles and related compounds from phenylhydrazones. Heating (**2**) in the presence of ***Zinc Chloride***, ***Formic Acid***/H_2SO_4, formic acid/HCl, or modified alumina catalysts provides 2-methylindole in modest to high yields. Indole formation is favored when anhydrous acid catalysts are used at high temperature to promote formation of the ene-hydrazine intermediate (eq 3).[25,26] In addition, β-lactams[27] and triazolinones[28] have also been synthesized from (**2**). Some cyclic diaza compounds containing other heteroatoms have been prepared from phenylhydrazones. Cycloaddition with thiocyanates or ***Carbon Disulfide*** leads to the formation of substituted thiadiazolidines (eq 4).[29] Treating (**2**) with ***Phosphorus(III) Chloride*** or $AsCl_3$ results in the formation of diazaphosphole and diazaarsole in modest yields (eq 5).[30]



(3)

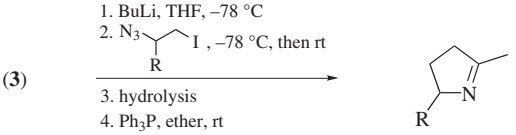


(4)



(5)

With (**3**) and other ketone dimethylhydrazones, formation of heterocycles occurs via annulation reactions of their condensation or alkylation products. The strategy involves either a Michael-type addition or 1,2-addition of the azaallyl anion of (**3**) to carbonyl compounds or esters followed by a ring closure step to afford dihydropyridines[31] and substituted pyridines.[32] 1-Pyrrolines have also been prepared in good yield by alkylation of the anion of (**3**) with ω-iodo azide followed by treatment with ***Triphenylphosphine*** (eq 6).[33]



(6)