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Handbook of Reagents for Organic Synthesis

Reagents for Heteroarene Synthesis

Edited by

André B. Charette
Université de Montréal, Montréal, Québec, Canada

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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

- *Acidic and Basic Reagents*
  Edited by Hans J. Reich and James H. Rigby

- *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

- *Reagents for High-Throughput Solid-Phase and Solution-Phase Organic Synthesis*
  Edited by Peter Wipf

- *Reagents for Glycoside, Nucleotide, and Peptide Synthesis*
  Edited by David Crich

- *Reagents for Direct Functionalization of C–H Bonds*
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  Edited by Philip L. Fuchs

- *Catalytic Oxidation Reagents*
  Edited by Philip L. Fuchs

- *Reagents for Heteroarene Functionalization*
  Edited by André B. Charette

- *Reagents for Organocatalysis*
  Edited by Tomislav Rovis

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*.

Philip L. Fuchs
Purdue University
West Lafayette, IN USA
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 imparted 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.

*André B. Charette*
*Université de Montréal, Montréal, Québec, Canada*
Recent Review Articles and Monographs

Recent Reviews


Majumdar, K. C.; Debnath, P.; Roy, B. Metal-catalyzed het-


Ruiz-Castillo, P.; Buchwald, S. L. Applications of palladium-

Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. 2-


Tanaka, K. Rhodium-Catalyzed catalyzed [2+2+2] Cycload-


Wasserman, H. H.; Parr, J. The chemistry of vicinal tri-

Wolfe, J. P.; Thomas, J. S. Recent developments in palladium-

Zhang, B.; Studer, A. Recent advances in the synthesis of ni-


Zula, A.; Kikeli, D.; Ilas, J. Chemistry of 2-

Selected Books


Avoid Skin Contact with All Reagents
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

<p>| 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-tert-butyl-p-cresol) |
| BINAL-H | 2,2'-dihydroxy-1,1'-binaphthyl-lithium aluminium hydride |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| BINOL | 1,1'-bi-2,2'-napthol                        |
| bipy | 2,2'-bipyridyl                              |
| BMS | borane-dimethyl sulfide                     |
| Bn  | benzyl                                      |
| Boc | tert-butoxycarbonyl                         |
| BOM | benzylloxy methyl                           |
| bp  | boiling point                               |
| Bs  | brosyl (4-bromobenzenesulfonyl)             |
| BSA | N,O-bis(trimethylsilyl)acetamide            |
| Bu  | n-butyl                                     |
| Bz  | benzoyl                                     |
| CAN | cerium(IV) ammonium nitrate                 |
| Cbz | benzylloxy carbonyl                         |
| CDI | N,N'-carbonyldimidazole                     |
| CHIRAPHOS | 2,3-bis(diphenylphosphino)butane         |
| Chx | =Cy                                         |
| cod | cyclooctadiene                              |
| cot | cyclooctatetraene                           |
| Cp  | cyclopentadien                              |
| CRA | complex reducing agent                      |
| CSA | 10-camphorsulfonic acid                     |
| CSI | chlorosulfonic acid                         |
| Cy  | cyclohexyl                                  |
| d   | density                                     |
| DABCO | 1,4-diazabicyclo[2.2.2]octane              |
| DAST | N,N'-diethylanisulfur trifluoride           |
| dba | dibenzylideneacetone                        |
| DBAD | di-tert-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 acetylene dicarboxylate            |
| 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-tert-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 | hexamethylenphosphoric triamide             |
| HOBt | 1-hydroxybenzotriazole                      |
| HOBt | =HOBt                                       |
| HOSu | N-hydroxy succinimide                       |
| 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 |</p>
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LDMAN</td>
<td>lithium 1-(dimethylamino)naphthalenide</td>
</tr>
<tr>
<td>LHMD5</td>
<td>=LiHMDS</td>
</tr>
<tr>
<td>LICA</td>
<td>lithium isopropylcyclohexylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>LiTMP</td>
<td>lithium 2,2,6,6-tetramethylpiperidide</td>
</tr>
<tr>
<td>LTMP</td>
<td>=LiTMP</td>
</tr>
<tr>
<td>LTA</td>
<td>lead tetraacetate</td>
</tr>
<tr>
<td>lut</td>
<td>lutidine</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>m-chloroperbenzoic acid</td>
</tr>
<tr>
<td>MA</td>
<td>maleic anhydride</td>
</tr>
<tr>
<td>MAD</td>
<td>methylaluminum bis(2,6-di-t-butyl-4-methylphenoxo)</td>
</tr>
<tr>
<td>MAT</td>
<td>methylaluminum bis(2,4,6-tri-t-butylphenoxo)</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MEK</td>
<td>methyl ethyl ketone</td>
</tr>
<tr>
<td>MEM</td>
<td>(2-methoxyethoxy)methyl</td>
</tr>
<tr>
<td>MIC</td>
<td>methyl isocyanate</td>
</tr>
<tr>
<td>MMPP</td>
<td>magnesium monoperoxysphthalate</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>MoOPH</td>
<td>oxodiperoxomolybdenum(pyridine)-(hexamethylphosphoric triamide)</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MMP</td>
<td>=PMB</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl (methanesulfonyl)</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry; molecular sieves</td>
</tr>
<tr>
<td>MTBE</td>
<td>methyl t-butyl ether</td>
</tr>
<tr>
<td>MTM</td>
<td>methylthiomethyl</td>
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<td>MVK</td>
<td>methyl vinyl ketone</td>
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<td>NaHDMS</td>
<td>sodium hexamethyldisilazide</td>
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<td>Naph</td>
<td>naphthyl</td>
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<tr>
<td>NBA</td>
<td>N-bromoacetamide</td>
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<td>nbd</td>
<td>norbornadiene (bicyclo[2.2.1]hepta-2,5-diene)</td>
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<td>NBS</td>
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<td>N-iodosuccinimide</td>
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<td>NMO</td>
<td>N-methylmorpholine N-oxide</td>
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<td>NMP</td>
<td>N-methyl-2-pyrrolidinone</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>NORPHOS</td>
<td>bis(diphenylphosphino)bicyclo[2.2.1]hepta-5-ene</td>
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<tr>
<td>Np</td>
<td>=Naph</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
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<td>PDC</td>
<td>pyridinium dichromate</td>
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<td>Piv</td>
<td>pivaloyl</td>
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<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PMDTA</td>
<td>N,N,N',N''-pentamethyldiethylene-triamine</td>
</tr>
<tr>
<td>PPA</td>
<td>polyphosphoric acid</td>
</tr>
<tr>
<td>PPE</td>
<td>polyphosphate ester</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluene sulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>n-propyl</td>
</tr>
<tr>
<td>PTC</td>
<td>phase transfer catalyst/catalysis</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluenesulfonic acid</td>
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<tr>
<td>py</td>
<td>pyridine</td>
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<tr>
<td>RAMP</td>
<td>(R)-1-amino-2-(methoxymethyl)pyrrolidine</td>
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<tr>
<td>rt</td>
<td>room temperature</td>
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<tr>
<td>salen</td>
<td>bis(salicylidene)ethylene diamine</td>
</tr>
<tr>
<td>SAMP</td>
<td>(S)-1-amino-2-(methoxymethyl)pyrrolidine</td>
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<tr>
<td>SET</td>
<td>single electron transfer</td>
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<tr>
<td>Sia</td>
<td>siamyl (3-methyl-2-butyl)</td>
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<tr>
<td>TASF</td>
<td>tris(diethylamino)sulfonium difluorotrimethylsilicate</td>
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<td>TBAB</td>
<td>tetrabutylammonium bromide</td>
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<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
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<tr>
<td>TBAD</td>
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<td>TBAI</td>
<td>tetrabutylammonium iodide</td>
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<tr>
<td>TBAP</td>
<td>tetrabutylammonium perruthenate</td>
</tr>
<tr>
<td>TBDMs</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDFS</td>
<td>t-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBHP</td>
<td>t-butyldihydroperoxide</td>
</tr>
<tr>
<td>TBS</td>
<td>=TBDMs</td>
</tr>
<tr>
<td>TCNE</td>
<td>tetracyanoethylene</td>
</tr>
<tr>
<td>TCNQ</td>
<td>7,7,8,8-tetracyanoquinodimethane</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TEBA</td>
<td>triethylbenzylammonium chloride</td>
</tr>
<tr>
<td>TEBAC</td>
<td>=TEBA</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethylpiperidinoxyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>TFF</td>
<td>tr triflyl (trifluoromethanesilyl)</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran; tetrahydropyranyl</td>
</tr>
<tr>
<td>Thx</td>
<td>thexyl (2,3-dimethyl-2-butyl)</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TMANO</td>
<td>trimethylamine N-oxide</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N''-tetramethylethenediamine</td>
</tr>
<tr>
<td>TMG</td>
<td>1,1,3,3-tetramethylguanidine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>p-tolyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>TBHP</td>
<td>t-butyldihydroperoxide</td>
</tr>
<tr>
<td>TPP</td>
<td>tetraphenylporphyrin</td>
</tr>
<tr>
<td>Tr</td>
<td>trityl (triphenylmethyl)</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl (p-toluene sulfonoyl)</td>
</tr>
<tr>
<td>TTN</td>
<td>thallium(III) nitrate</td>
</tr>
<tr>
<td>UHP</td>
<td>urea–hydrogen peroxide complex</td>
</tr>
<tr>
<td>Z</td>
<td>=Cbz</td>
</tr>
</tbody>
</table>
Acetaldoxime

\[
\text{C}_2\text{H}_5\text{NO} \quad (MW \ 59.07)
\]

\text{InChI} = 1/C2H5NO/c1-2-3-4/h2,4H,1H3/b3-2-
\text{InChIKey} = FZENGILVLUJGJX-IHWYPQMZBM

\text{InChI} = 1/C2H5NO/c1-2-3-4/h2,4H,1H3/b3-2+
\text{InChIKey} = FZENGILVLUJGJX-NSCUHMNNBP

\text{InChI} = 1/C2H5NO/c1-2-3-4/h2,4H,1H3
\text{InChIKey} = FZENGILVLUJGJX-UHFFFAOYAK

\[\text{Acetaldoxime}\]

Solubility: soluble in most organic solvents, e.g. THF, CHCl.

Form Supplied in: widely available commercially. Commercial samples, which had been refrigerated for several months, showed (Z):(E) ratios of 10–20:1.\(^\text{1}\)

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).\(^\text{3,4,11}\)

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{(E)} & \quad \text{(Z)}
\end{align*}
\]

\[
\text{Acetaldoxime = H}_2\text{C} = \text{NOH} + \text{HCl} + \text{NaOH} \rightarrow \text{H} \quad \text{N} \\
\Delta, \text{1 h} \quad \text{H}_2\text{O} \\
\text{NaOH} \\
\text{E} + \text{Z}
\]

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,\(^\text{12}\) but the position of the equilibrium is independent of the temperature and the concentration of the acid.\(^\text{12}\) (Z)-Acetaldoxime can be prepared by slow crystallization of a freshly distilled mixture of (E)/(Z) isomers.\(^\text{13}\) \(^1\)H NMR\(^\text{11,14}\) and \(^1\)C NMR\(^\text{15}\) 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).\(^\text{1}\)

\[
\begin{align*}
\text{ArN}_2+\text{Cl}^- & \rightarrow \text{H}_2\text{O}^+ \\
\text{Acetaldoxime} & \rightarrow \text{Ar} \quad \text{H}
\end{align*}
\]

\[\text{(2)}\]

\[\text{Ar} \quad \text{H} \quad \text{Ar} \quad \text{O} \quad \text{H} \quad \text{N} \quad \text{M} \quad \text{R}
\]

**α-Alkylation of Acetaldoxime.** Deprotonation of acetaldoxime with 2 equiv of \textit{n-Butyllithium} at \(-78^\circ\text{C}\) generates the dianion which reacts with \textit{Benzy1 Bromide} or 1-iodopropane to give excellent yields of \(\alpha\)-alkylated (Z)-oximes (eqs 3 and 4).\(^\text{2}\) \(\alpha,\alpha\)-Dialkylation by further alkylation in similar way has been achieved (eq 4).\(^\text{2}\) It is generally known that ketone oximes can be deprotonated and alkylated regioselectively \textit{syn} to the oxime hydroxy group.\(^\text{16,17}\) It is essential to perform the deprotonation and alkylation at \(-78^\circ\text{C}\) as otherwise no \(\alpha\)-alkylated oximes are isolated, the major byproducts being nitriles.\(^\text{16}\)

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{H}_2\text{O} & \quad \text{Cl} \\
\text{Ar} & \quad \text{N} \\
\text{R} & \quad \text{H}_3\text{O}^+ \text{ArN}_2+\text{Cl}^- \\
\text{1. 2 n-ButLi, THF} & \rightarrow \text{R} = \text{CH}_2\text{Ph, n-Pr}
\end{align*}
\]

\[\text{(3)}\]

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{H}_2\text{O} & \quad \text{Cl} \\
\text{Ar} & \quad \text{N} \\
\text{R} & \quad \text{H}_3\text{O}^+ \text{ArN}_2+\text{Cl}^- \\
\text{1. 2 n-ButLi, THF} & \rightarrow \text{R} = \text{CH}_2\text{Ph, n-Pr}
\end{align*}
\]

\[\text{(4)}\]

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

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{H}_2\text{O} & \quad \text{Cl} \\
\text{Ar} & \quad \text{N} \\
\text{R} & \quad \text{H}_3\text{O}^+ \text{ArN}_2+\text{Cl}^- \\
\text{1. xylene} & \rightarrow \text{Ar} \quad \text{O} \quad \text{H} \quad \text{N} \quad \text{M} \\
\text{73–83%} & \quad \text{R}
\end{align*}
\]

\[\text{(5)}\]
Synthesis of Heterocycles. Chlorination of acetaldoxime with N-Chlorosuccinimide or Chlorine gas 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). 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).

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

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). Functionalization at the oxygen atom has been accomplished with organogergermanium and organoarsenium reagents (eq 16), while O-alkylation has been performed with the sodium salt of acetaldoxime and an α-bromo ketone. Lithium Aluminum Hydride readily effected hydrogenolysis of the N–O bond to afford the corresponding 1,2-diol (eq 17).

A list of General Abbreviations appears on the front Endpapers.
**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.

### 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).\(^{29}\)

\[
\text{H}_2\text{N} \begin{array}{c}
\text{COOR} \\
\text{X}
\end{array} \xrightarrow{1. \text{NaNO}_2, 37\% \text{HCl}, 0 \degree \text{C}} \xrightarrow{2. \text{MeCH}=\text{NOH}, \text{CuSO}_4*5\text{H}_2\text{O}} \text{AcONa, 10 - 15 \degree \text{C}} \xrightarrow{37\% \text{HCl \ reflux}} 42\%
\]

\(R = \text{Me, Et}; \ X = \text{NO}_2, \text{COOMe}\)

1. **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).\(^{30,31}\)

\[
\xrightarrow{[\text{O}]} \xrightarrow{Z=C\equiv\text{C}} [\text{C=N}^+\text{O}^-] \xrightarrow{Z=\text{Ph}} 35-93%
\]

\([\text{O}] = \text{NCS, Oxone}\)

\(Z = \text{Ph}; \) residue of 17-hydroxy-steroids (estrone series)

1. **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 \(N\)-methylmaleimide (NMM) to give substituted dihydro-2H-pyrrrol[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 \(\text{exo-}\) and \(\text{endo-}\)isomers (3:4:1) of 7-methyl-1-aza-8-oxabicyclo[3.2.1]octan-4-ones (eq 21).\(^{33}\)

\[
\xrightarrow{\text{exo-}} 59\% \xrightarrow{\text{endo-}} 36\%
\]

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.\(^ {40}\)

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.\(^ {40}\)

### Synthesis of Heterocycles

Acetaldoxime was used to synthesize \(3\beta\)-(substituted phenyl)\)-2\(\beta\)-isoxazol-5-yI-tropanes\(^ {41}\) (eq 23) and 5-propyl-4,5-dihydroisoxazole from the aliphatic \(\alpha,\beta\)-unsaturated aldehyde in the presence of an anilinium salt catalyst (eq 24).\(^ {42}\)

Avoid Skin Contact with All Reagents
The reactions of tetracyanospircyclopropane 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). Functionalization. O-Functionalization of acetaldoxime was performed by 2-chloroethyl vinyl ether, (24) N-methyl-2-chloromethylpyrrolidine, (25) vinyl glycidyl ether, (26) and 4-methylene-oxetan-2-one (27) (eq 26).
N-Alkylation of acetaldoxime with the formation of nitrone was used in the synthesis of $N$-hydroxy- and $N$-$\alpha$-cyanoethylamino acid methyl esters via the so-called 'acetaldoxime route' (eq 27).\(^{48}\)

\[
\begin{align*}
\text{N} \text{OH} & + \text{R} \text{O} \text{Me} \xrightarrow{\text{MeONa MeOH}} \text{Et}_{2} \text{AlCN} \\
\text{NC} & \text{N} \text{O} \text{Me} \\
\text{R} & = \text{Me, Ph} \\
\text{31–32%} & \\
\text{R} & = \text{Me} \\
\text{13%} & 
\end{align*}
\]

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).\(^{51}\)

\[
\begin{align*}
\text{N} \text{OH} & \xrightarrow{\text{HZ}} \text{NH}_{2} \\
\text{HZ} & = \text{Bronsted acid site of zeolite} \\
\text{HZ} = \text{H}^{+} \text{OH} \text{Z}^{-} & \\
\text{HZ} = \text{HZ}^{-} & \\
\text{HZ} = \text{Bronsted acid site of zeolite} & \\
\text{HZ} = \text{HZ}^{-} & \\
\end{align*}
\]

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).\(^{52}\)

\[
\begin{align*}
\text{N} \text{OH} & + \text{Et} \text{C} \text{N} \xrightarrow{\text{CH}_2\text{Cl}_2} \text{Cl} \text{Cl} \\
\text{HO} & \xrightarrow{\text{Et}} \text{Cl} \text{Cl} \\
\end{align*}
\]

Avoid Skin Contact with All Reagents
In CDCl$_3$ solution, the imino complex undergoes the spontaneous imine ligand dissociation to afford the carbonyl oxide complex trans-[PtCl$_2$(NH=CH(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).\(^{55}\) Acetaldoxime serves as an efficient water surrogate that delivers water to the substrate nitrile.

\[
\begin{align*}
R - \text{C} = \text{N} + N\text{OH} & \xrightarrow{\text{Pd(OAc)$_2$/PPh$_3$}} R - \text{NH$_2$} + N\text{C}=\text{O}.
\end{align*}
\]

An equilibrium oxime–carbonyl transformation in silica gel-supported liquid catalysts and water media was reported (eq 32).\(^{54,55}\)

\[
\begin{align*}
N\text{OH}^{-} + O & \xrightarrow{\text{H}_2\text{O, ionic liquid}} \text{silica gel, rt. 96 h} \xrightarrow{\text{O}} N\text{OH}^{-} + \text{O}^{-}
\end{align*}
\]

**Reduction.** Earlier reports reveal that catalytic transfer hydrogenation of oximes to amines had been achieved with systems such as ammonium formate/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).

\[
\begin{align*}
\text{Mg/HCOONH$_4$}, \text{MeOH, rt, 40 min} & \xrightarrow{\text{N\text{OH}^{-}}} \text{Et$_3$SiH, CHCl$_3$} \xrightarrow{\text{66\%}} \text{NH$_2$OH}.
\end{align*}
\]

**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 (E)-CH$_2$CH=NH-OH and (Z)-CH$_2$CH=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; Hydroxy-lamine; 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.

Acetone Hydrazone\(^1\)

\[
R^1 = R^2 = H
\]

\[
[5281-20-9]
\]

\[
C_5H_12N_2
\]

\[(MW 72.11)\]

\[
\text{InChI} = 1/C_5H_{12}N_2/c1-5(2)6-7(3)4/h1-4H3
\]

\[
\text{InChIKey} = JIQKYSNGXUDJU-UHFFFAOYAV
\]

\[(2; R^1 = H, R^2 = Ph)\]

\[
[103-02-6]
\]

\[
C_9H_{12}N_2
\]

\[(MW 148.21)\]

\[
\text{InChI} = 1/C_9H_{12}N_2/c1-8(2)10-11-9-6-4-3-5-7-9/h3-7,11H,
\]

\[1-2H3\]

\[
\text{InChIKey} = JQLKSEQEJILJEG-UHFFFAOYAR
\]

\[(3; R^1 = R^2 = Me)\]

\[
[13483-31-3]
\]

\[
C_5H_{12}N_2
\]

\[(MW 100.17)\]

\[
\text{InChI} = 1/C_5H_{12}N_2/c1-5(2)6-7(3)4/h1-4H3
\]

\[
\text{InChIKey} = IDSMDKUVIBSETN-UHFFFAOYAD
\]

(metalated dimethylhydrazones as anion equivalents are especially useful for regioselective alkylations\(^4,5\) and as precursors of unsymmetrical ketone hydrazones;\(^1,3\) gem-dimethyl synths in cycloaddition reactions\(^6\))

**Physical Data:** (1) \(n^2_0 = 1.4607\), 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).  

**Solubility:** sol alcohol, ether, THF, CH\(_2\)Cl\(_2\).

**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.\(^8,9\) 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).\(^4,9\) 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.\(^9,10\) The dimethylhydrazine can be prepared in very high yield by a general procedure for ketones using anhydrous N,N-Dimethyldihydrazine.\(^5,6\) 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; disproportionate 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.\(^9\) Azine formation is rapid in the

---

**Acetone Hydrazone**

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**Handling, Storage, and Precautions:** (1) usually prepared just before use; unstable in the pure liquid state; disproportionate 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.\(^9\) Azine formation is rapid in the
Hydrazone Oxidations. The reactions of ketone hydrazones depend largely on the degree and kind of substitution on the N-amino group. Hydrazone (1) (R1 = R2 = 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. The latter undergoes 1,3-cycloaddition reactions with electrophilic C==C bonds to form substituted pyrazoles,14 vinyl and epoxy quinones,12 and pyrazolines.13 With Diphenylketone acetylene a pyrazole is formed that can be subsequently photolyzed to a conjugated alkynylcyclopropane.

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 Benzeneeliminyl Bromide in the presence of a hindered guanidine base to afford phenyl vinyl selenide 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

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,20 Sodium Perborate, Sodium Periodate, and H2IO.28 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. Carbon monoxide from (1) affords aminooximinoalkylcarboxylates.23 An alternative to the Pictet–Robinson pyrrole synthesis has been used by Baldwin to prepare pyrroles from any enolizable aldehyde or ketone via azines synthesized from the corresponding hydrazones. The reaction is shown for (1) (eq 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/H2SO4, 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-lactams27 and triazolinones28 have also been synthesized from (2). Some cyclic diaza compounds containing other heteroatoms have been prepared from phenylhydrazones. Cycloaddition with thiocyanates or Carbon Dioxide leads to the formation of substituted thiadiazolidines (eq 4).29 Treating (2) with Phosphorus(III) Chloride or AsCl3 results in the formation of diazophosphole and diazaazasole in modest yields (eq 5).30

Acid cat, heat

Acid cat, heat

Acid cat, heat

Acid cat, heat

Acid cat, heat

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 azaaalyl anion of (3) to carbonyl compounds or esters followed by a ring closure step to afford dihydropyridines31 and substituted pyridines.32 1-Pyrrolines have also been prepared in good yield by alkylation of the anion of (3) with α-iodo azide followed by treatment with Triphenylphosphine (eq 6).33

A list of General Abbreviations appears on the front Endpapers