

ENCYCLOPEDIA

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*R e a g e n t s*

*for*

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*S y n t h e s i s*

*Editor-in-Chief*  
Leo A. Paquette

Volume 1

**A - Bru**



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# Preface

The extent to which organic synthetic methodology has developed and flourished during the past several decades has placed unusually heavy demands on the broad range of scientists who utilize chemical reagents. There exists the vital need to know which reagent will perform a specific transformation. Since a number of reagents are often amenable to similar objectives, a researcher's ability to access readily a comparative summary of those features that distinguish one reagent from another can result in a considerable economy of time. The purpose of the *Encyclopedia of Reagents for Organic Synthesis* is to incorporate into a single work a genuinely authoritative and systematic description of the utility of all reagents used in organic chemistry. Its comprehensiveness is further served by an unrivaled ease to locate any specific entry or topic.

These objectives have been met by inviting practicing chemists from throughout the world to provide specific contributions in their area of expertise. Furthermore, the masthead for each of the 3000 reagents provides valuable information concerning physical data, solubility, form supplied in, purification, and, where relevant, preparative methods. The CAS registry number, handling/storing information, and precautions will further serve potential users. The first literature reference in each entry provides reviews, if available, dealing with the subject reagent. The critical coverage of all relevant literature is extensive.

The goal of the *Encyclopedia of Reagents for Organic Synthesis* is to serve as a reference work where the retrievability of useful information concerning any specific reagent is made facile. For this reason there is a detailed subject index and, in addition, a formula index of all the reagents, and also two further indexes that list the reagents by structural class and by function.

In any undertaking of this type, it is important that the term 'reagent' be clearly defined. The guideline that has dominated the thinking of the members of the Editorial Board is that a reagent be an agent or a combination of agents which with some generality effects the transformation of a substrate into a product. In addition, many useful building blocks have been included. As a consequence, we anticipate that a work has been produced that will serve biochemists, material scientists, pharmacologists, and chemical engineers, in addition to chemists from all disciplines, in that manner most conducive to accelerating progress in their respective fields of research.

The entries highlight the various uses characteristic of each reagent, with specific examples illustrative of these chemical reactions. The contributions are organized alphabetically and the cross-referencing to other reagents is liberal. Thus, a concerted effort has been made to bring together in one place a detailed compilation of the uses of those reagents that will serve both the beginning and experienced investigator. The wealth of facts contained within the *Encyclopedia of Reagents for Organic Synthesis* has been assimilated in a manner which will cause all scientists to want this source of information kept in close proximity to their laboratory.

A work of this magnitude could not have been brought to realization without the input of a great deal of time, effort, and dedication on the part of a large number of highly responsible individuals. I am especially indebted to the editors – Steven Burke, Robert Coates, Rick Danheiser, Scott Denmark, David Hart, Lanny Liebeskind, Dennis Liotta, Anthony Pearson, Hans Reich, James Rigby, and William Roush – for their tremendously valuable enthusiasm, intensive work, and unstinting persistence. A most critical role has been played by Colin Drayton, not only in conceiving the project but also as a consequence of his range of knowledge of the publishing business in steering us continually in the proper direction and in overseeing the massive editing operation. James Edwards and Mark Volmer are also to be thanked for their central role as assistant section editors. The body of this encyclopedia was composed by over 1000 authors from 40 countries around the world. The knowledge and expertise contributed by these experienced investigators in the form of authoritative treatises dealing with reagents with which they are thoroughly familiar constitutes the scientific underpinning of the entire undertaking. The enlightening end product of their contributions will have a major impact on the conduct of research in organic chemistry and I thank each of these individuals for their insightful entries.

The large contingent of organic chemists alluded to above, directly and indirectly, expects the *Encyclopedia of Reagents for Organic Synthesis* to play a vital role in stimulating creative research in organic chemistry in the years immediately ahead. All of us hope that you will share in this excitement by perusing its many pages and creatively adapting the valuable information contained therein.

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# Foreword

This Encyclopedia covers comprehensively over 3000 reagents, alphabetically arranged using IUPAC nomenclature. The articles are self-contained but ***Bold Italics*** are used within each article to indicate other reagents that have their own entries in the Encyclopedia. A list of related reagents is given at the end of articles.

Although most articles are devoted to a single reagent, in some cases closely related reagents are covered under one heading, e.g. Methyl Trimethylsilylacetate is discussed in the article on Ethyl Trimethylsilylacetate, and Lithium Trimethoxyaluminum Hydride in the article on Lithium Tri-*t*-butoxyaluminum Hydride.

A particular reagent can be found either directly, by going to the appropriate place in the Encyclopedia, or from the Subject Index in Volume 8. Numerous other topics, such as

types of reaction, named reactions, named reagents, general substrates or products, and specific substrates or products, are included in this index.

Volume 8 also contains a Formula Index, listing all reagents covered in the Encyclopedia.

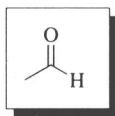
In addition, there are two further compilations of all the reagents in Volume 8, a Reagent Structural Class Index and a Reagent Function Index. The former groups the reagents under headings such as Dienes, Hydrides, and Titanium Reagents, while the latter has headings such as Alkylating Agents, Desilylation Reagents, and Ring Expansion Agents.

The abbreviations used for journals in the references are on the front endpapers of all volumes, while the back endpapers list other abbreviations used throughout the Encyclopedia.



# A

## Acetaldehyde



[75-07-0]

C<sub>2</sub>H<sub>4</sub>O

(MW 44.05)

(reagent used as two-carbon electrophilic component in a wide array of reactions)

**Physical Data:** mp -123.5 °C; bp 21 °C; *d* 0.788 g cm<sup>-3</sup>.

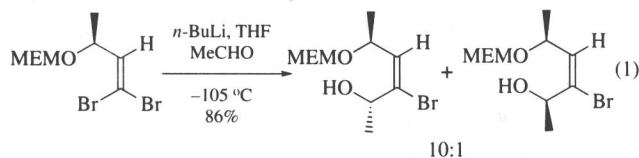
**Solubility:** sol H<sub>2</sub>O, alcohol, ether, and most organic solvents.

**Form Supplied in:** colorless liquid; widely available.

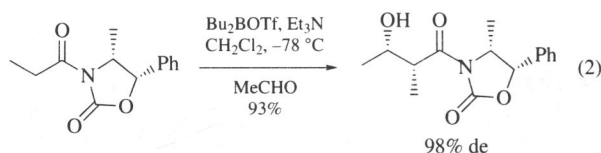
**Purification:** shaken with powdered NaHCO<sub>3</sub> for 30 min; dried over CaSO<sub>4</sub>, and fractionally distilled at 760 mmHg through a 70 mm Vigreux column.

**Handling, Storage, and Precautions:** bottles may develop pressure and should be cooled before opening. To help prevent polymerization and autoxidation, store under nitrogen atmosphere and refrigerate. Acetaldehyde is a cancer suspect agent and should be used only in a well-ventilated fume hood. Toxicity (oral) rat LD<sub>50</sub>: 661 mg kg<sup>-1</sup>. Incompatible with strong acids, strong bases, oxidizing and reducing agents. Decomposes on prolonged exposure to air.

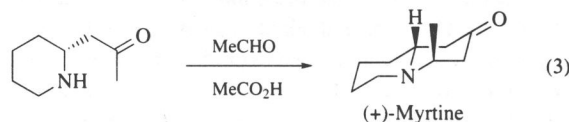
**1,2-Additions.** Acetaldehyde reacts with a myriad of nucleophilic reagents, generally providing excellent yields of the two-carbon extended secondary alcohols. Aryl-,<sup>1</sup> alkynyl-,<sup>2</sup> and alkylolithiums<sup>3</sup> react rapidly with acetaldehyde even at low temperature. A chiral vinylolithium reagent at low temperature reacts stereoselectively to afford a 10:1 mixture of diastereomeric alcohols (eq 1).<sup>4</sup> Aryl<sup>5</sup> or alkyl<sup>6</sup> Grignard reagents behave in an analogous manner with acetaldehyde to give the secondary alcohols or the methyl ketones<sup>7</sup> upon subsequent oxidation. Allyl organometallics react with varying degrees of stereocontrol depending on the metal and conditions to give the corresponding homoallylic alcohols.<sup>8</sup> Chiral allylboronates also react with acetaldehyde at -78 °C to afford the homoallylic alcohols with high enantioselectivity.<sup>9</sup> *trans*-Epoxides are produced selectively through the Darzens reaction of acetaldehyde with halomethyl sulfones under basic phase transfer conditions.<sup>10</sup> Classical Wittig reagents<sup>11</sup> and Horner-Emmons phosphonate<sup>12</sup> ylides react with acetaldehyde to give the alkene.



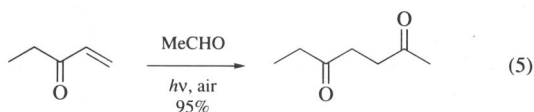
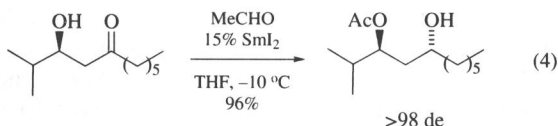
**Aldol Additions.** Acetaldehyde serves as an electrophilic partner in the aldol condensation with a wide array of enolates.<sup>13</sup> Knoevenagel condensation of acetaldehyde with active methylene compounds in the presence of base provides good yields of the ethylidene substituted compounds.<sup>14</sup> Addition of two equivalents of an active methylene compound to acetaldehyde results in a Michael addition of the second equivalent to the initially formed ethylidene.<sup>15</sup> Tollens reaction of acetaldehyde with formaldehyde gives pentaerythritol.<sup>16</sup> The addition of acetaldehyde in a Baylis-Hillman condensation with *Ethyl Acrylate* using **1,4-Diazabicyclo[2.2.2]octane** (DABCO) as catalyst gives a 90% yield of the allylic alcohol.<sup>17</sup> The stereoselective aldol reaction of acetaldehyde with achiral<sup>18</sup> and chiral<sup>19</sup> imide enolates has received much attention and is a proven method for controlling acyclic relative and absolute stereochemistry.<sup>13</sup> For example, the boron enolate of a norephedrine-derived propionyloxazolidine reacts with acetaldehyde to afford in 90% yield and >98% de the *syn* aldol product (eq 2).<sup>19a</sup> Acetaldehyde also smoothly undergoes nitro-aldol condensation to the corresponding nitro alcohols.<sup>20</sup> The lithium enolates of a variety of heterocycles react with acetaldehyde to give good yields of product alcohols.<sup>21</sup> In addition, the zinc,<sup>22</sup> copper,<sup>23</sup> and boron<sup>24</sup> enolates of esters and ketones provide aldol products with acetaldehyde.



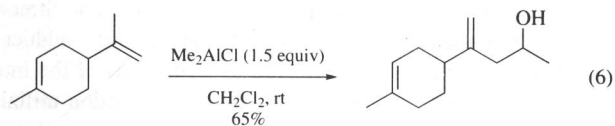
**Mannich and Mannich-Type Reactions.** Although not as commonly used as **Formaldehyde**, acetaldehyde undergoes many synthetically useful Mannich reactions. Intramolecular Mannich reaction of acetaldehyde has been utilized to produce the natural product myrtine (eq 3).<sup>25</sup> The intramolecular Mannich reaction has also been used in the synthesis of proline derivatives.<sup>26</sup> Nucleophiles as diverse as dialkyl phosphites<sup>27</sup> and amines<sup>28</sup> or aryl radicals<sup>29</sup> may also add to the intermediate imine of acetaldehyde in Mannich-type reactions. A historically significant reaction of acetaldehyde in this mode is the Strecker synthesis of alanine, whereby cyanide is added to the adduct of ammonia and acetaldehyde followed by hydrolysis of the intermediate  $\alpha$ -aminonitrile.<sup>30</sup> The Pictet-Spengler reaction utilizing acetaldehyde is an important ring-forming reaction. Acetaldehyde has been extensively used in the synthesis of the biologically active  $\beta$ -carbolines from tryptophan derivatives through this cyclization.<sup>31</sup> Other ring systems such as tetrahydroisoquinolines<sup>32</sup> and dihydrooxazines<sup>33</sup> have also been formed employing Pictet-Spengler cyclization with acetaldehyde.



**Metal and Other Promoted Condensations.** In the mixed Tishchenko reaction using *Aluminum Isopropoxide* as promoter, acetaldehyde is predominately the oxidized partner. Thus when condensed with benzaldehyde, benzyl acetate is the major product.<sup>34</sup> Recently an interesting and synthetically useful stereoselective intramolecular Tishchenko reduction of  $\beta$ -hydroxy ketones using acetaldehyde and promoted by *Samarium(II) Iodide*, affording *anti*-1,3-diol monoacetates, has been reported (eq 4).<sup>35</sup> The stereoselective pinacol cross-coupling of acetaldehyde with other higher-order aldehydes that contain chelating functionalities has been achieved using a vanadium(II) reagent.<sup>36</sup> The photochemical addition of acetaldehyde in the presence of molecular oxygen to  $\alpha,\beta$ -unsaturated esters and ketones provides excellent yields of the 1,4-dicarbonyl compounds (eq 5).<sup>37</sup>



**Pericyclic Reactions.** The thermal ene reactions of acetaldehyde and other aliphatic aldehydes with alkenes are generally not very productive.<sup>38</sup> However, acetaldehyde can be induced to undergo ene reactions with a variety of alkenes under Lewis acid activation. *Dimethylaluminum Chloride* has been used to promote the ene reaction between the relatively reactive 1,1-di-, tri-, and tetrasubstituted alkenes (eq 6).<sup>39</sup> With the more unreactive monosubstituted terminal alkenes, the more Lewis acidic *Ethylaluminum Dichloride* must be employed to obtain reasonable yields of ene products with acetaldehyde.<sup>40</sup> Acetaldehyde is a relatively unreactive dieneophile towards dienes. The hetero-Diels–Alder reaction of acetaldehyde has been reported under high pressure acceleration with 1-alkoxydienes to afford good yields of dihydropyrans with modest *endo* selectivity.<sup>41</sup>



**Paraldehyde and Other Acetaldehyde Derivatives.** Paraldehyde has historically been used as a stable and less volatile form of acetaldehyde in a wide array of chemical reactions.<sup>42</sup> However, since its classification as a controlled substance, its restricted availability has led to its limited use in modern synthetic organic chemistry. Acetaldehyde can be generated from paraldehyde through acid catalyzed degradation of the trimer and isolated by distillation.<sup>43</sup> The diethyl acetal of acetaldehyde, commonly known as acetal, may be generated from acetaldehyde or paraldehyde, ethanol, and calcium chloride.<sup>44</sup> Acetaldehyde and

paraldehyde have also been used for the protection of diols as their ethylidene acetals.<sup>45</sup>

**Related Reagents.** Acetaldehyde *N*-*t*-Butylimine; Acetaldoxime; Crotonaldehyde; Dimethylaluminum Chloride; Ethyl Vinyl Ether; Formaldehyde; Formaldehyde–Dimethylamine; Vinyl Acetate.

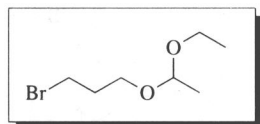
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## Acetaldehyde 3-Bromopropyl Ethyl Acetal



[34399-67-2]

C<sub>7</sub>H<sub>13</sub>BrO<sub>2</sub>

(MW 211.1)

(electrophilic or nucleophilic hydroxypropylation reagent<sup>1</sup>)

Alternate Name: 1-bromo-3-(1-ethoxyethoxy)propane.

**Physical Data:** colorless liquid, bp 49–51 °C/1 mmHg.<sup>1</sup>

**Solubility:** sol common organic solvents (i.e. diethyl ether, THF, 1,3-propanediol).

**Analysis of Reagent Purity:** <sup>1</sup>H NMR.

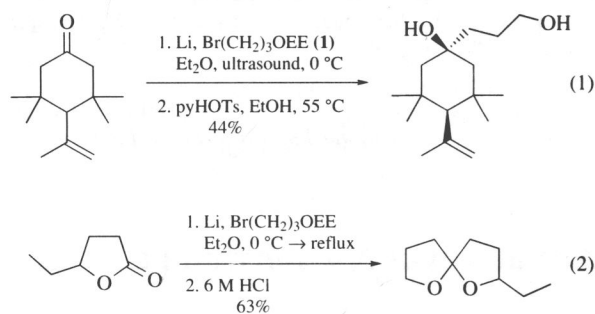
**Preparative Method:** the reagent has been prepared from 3-bromo-1-propanol and **Ethyl Vinyl Ether** using dichloroacetic acid as the catalyst.<sup>1</sup> The choice of the catalyst was reported to be crucial to the success of the procedure. This preparation provided the product in 92% yield.

**Purification:** purification was performed by vacuum distillation, bp 49–51 °C/1 mmHg.<sup>1</sup>

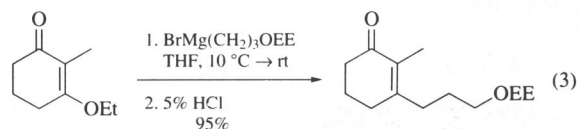
**Handling, Storage, and Precautions:** the reagent is acid sensitive and is stored at –30 °C over powdered sodium carbonate.<sup>1</sup> This is an alkylation reagent; proper protective equipment should be worn and use restricted to a fume hood.

**Introduction.** Acetaldehyde 3-bromopropyl ethyl acetal (**1**) has been utilized as an electrophilic 3-bromo-1-propanol equivalent and as a source of a nucleophilic three-carbon hydroxypropyl synthon.

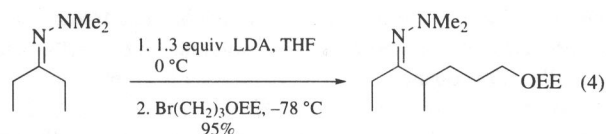
**Nucleophilic Addition.** 1-Lithio-3-(1-ethoxyethoxy)propane, prepared from (**1**) and **Lithium** in diethyl ether, has been added to aldehydes,<sup>2</sup> ketones (eq 1),<sup>1,3</sup> lactones (eq 2),<sup>4</sup> lactams,<sup>5</sup> and chlorosilanes.<sup>6</sup> Although the THP ether has also been utilized, the ethoxyethyl ether is hydrolyzed under milder conditions.<sup>7</sup> The corresponding organocopper reagent has been added to α,β-unsaturated ketones and alkyl halides.<sup>8,9</sup>



The Grignard reagent prepared from (**1**) has been added to β-alkoxy enones (eq 3) and coupled with allylic bromides.<sup>10–12</sup>



**Alkylation.** Carbanions derived from *N,N*-dimethylhydrazones have been alkylated with (**1**) (eq 4).<sup>13,14</sup> The hydrolysis conditions utilized to regenerate the ketone do not allow for the isolation of the protected alcohol product. This can be overcome with the THP ether.<sup>14</sup> Multifunctionalized ethers have also been synthesized using (**1**).<sup>15</sup>

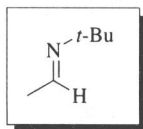


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## Acetaldehyde *N*-*t*-Butylimine



[7020-80-6]

C<sub>6</sub>H<sub>13</sub>N

(MW 99.17)

(E)

[62058-77-9]

(acetaldehyde equivalent; synthesis of  $\alpha,\beta$ -unsaturated aldehydes)

**Alternate Names:** *N*-ethylidene-1,1-dimethylethylamine; *N*-(ethylidene)-*t*-butylamine; *N*-ethylidene-2-methyl-2-propanamine.

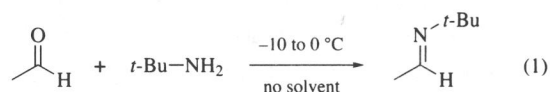
**Physical Data:** bp 25–28 °C/95 mmHg;  $n_D^{19.2}$  1.4005.

**Solubility:** sol most organic solvents.

**Form Supplied in:** colorless liquid; not commercially available.

**Analysis of Reagent Purity:** <sup>1</sup>H NMR; GC.

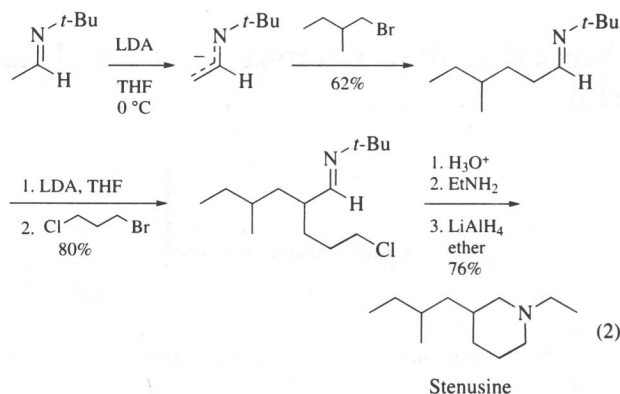
**Preparative Methods:** condensation of freshly distilled **Acetaldehyde** with ***t*-Butylamine** without solvent.<sup>1–4</sup> The way the reactants are mixed is crucial. *t*-Butylamine is added dropwise to 1 equiv of the aldehyde at –10 to 0 °C (eq 1). The reaction mixture is further stirred at rt for 10 min after which solid KOH is added (about 10 g per mol). After separation of the water layer, the imine is distilled over KOH using a Vigreux column. It was reported that azeotropic removal of the water, formed during the reaction, with an organic solvent, nonmixable with water, gave good results.<sup>5</sup> However, it was found that this procedure with dichloromethane as solvent gave an end product which was always contaminated with the solvent.<sup>4</sup>



**Handling, Storage, and Precautions:** very sensitive to hydrolysis; store in closed vessels under an inert atmosphere in the refrigerator. Use of the freshly distilled reagent is recommended. Use in a fume hood.

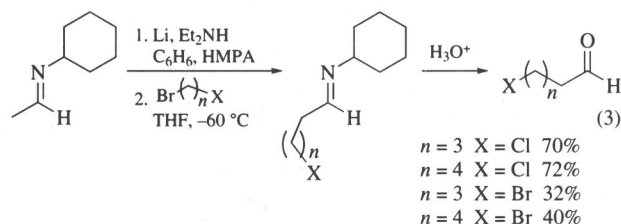
**Introduction.** Imines derived from acetaldehyde and lower alkylamines, e.g. ethylamine, are extremely difficult to handle under basic reaction conditions.<sup>6</sup> More bulky derivatives such as acetaldimines derived from cyclohexylamine and preferably *t*-butylamine are much more stable and can be used as a ready acetaldehyde equivalent.

**Reactions of Metalated Acetaldehyde *N*-*t*-Butylimine.** Lithiation of aldimines results in a change from (*E*) to (*Z*) configuration.<sup>7</sup> A facile carbon–carbon bond rotation in 1-azaallyl-lithium reagents is readily observed by variable temperature <sup>1</sup>H NMR spectroscopy.<sup>8</sup> Lithiation is most frequently performed by **Lithium Diisopropylamide** or **Lithium Diethylamide** in THF or diethyl ether. Lithiated acetaldehyde *t*-butylimine is readily  $\alpha$ -monoalkylated by alkyl bromides, but  $\alpha,\alpha$ -dialkylation is difficult to avoid.<sup>4</sup> This acetaldimine has been used to prepare the alkaloid stenusine, the spreading agent of the beetle *Stenus comma* (eq 2).<sup>4,9</sup> Attempts to perform the synthesis starting from acetaldehyde *N*-ethylimine failed.<sup>4</sup>

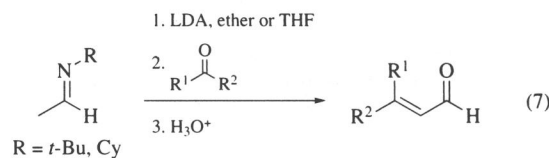
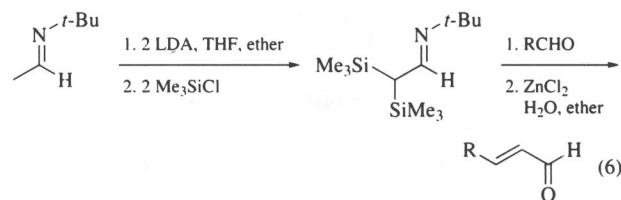
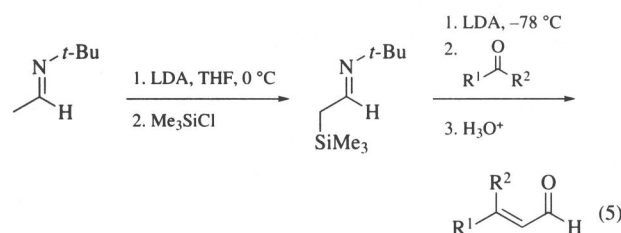
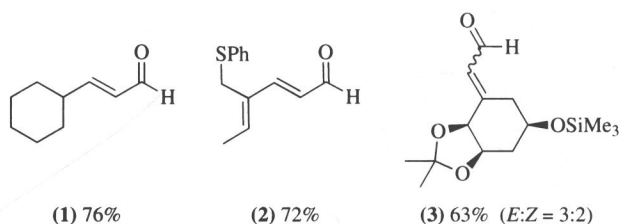
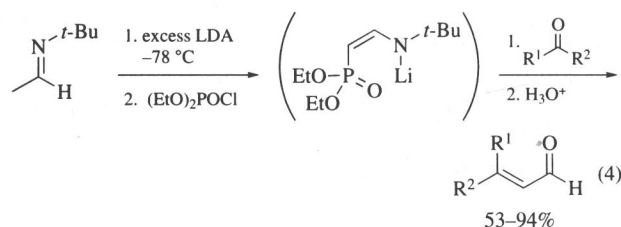




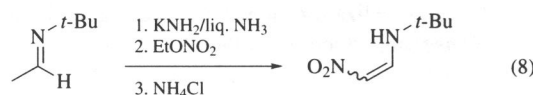
Similar  $\alpha$ -deprotonations and  $\alpha$ -alkylations of acetaldehyde cyclohexylimine have been performed with **Potassium-Graphite** and alkyl bromides, respectively.<sup>10</sup>  $\omega$ -Halo aldehydes (eq 3),<sup>11</sup> 4-bromo-4-pentalen,<sup>12</sup> and 5-chloro-4-alkenals<sup>12</sup> are accessible from the same aldimine after deprotonation and reaction with  $\alpha,\omega$ -dihaloalkanes, **2,3-Dibromopropene**, and 3-chloroallyl chloride, respectively.



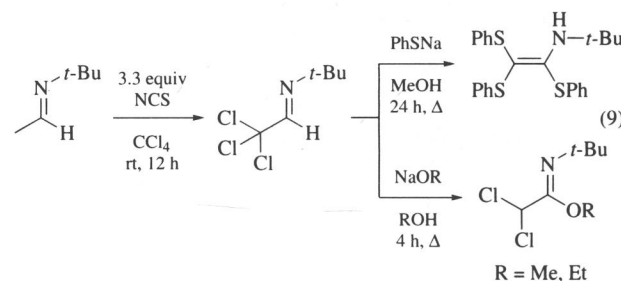
Acetaldehyde *t*-butylimine is an extremely versatile building block for the synthesis of  $\alpha,\beta$ -unsaturated aldehydes by lithiation, subsequent reaction with diethyl chlorophosphate, further reaction with aldehydes or ketones, and final hydrolysis (eq 4).<sup>13</sup> Examples include 3-cyclohexylpropenal (**1**),<sup>13</sup> (*E,E*)-4-(phenylthiomethyl)-2,4-hexadienal (**2**),<sup>14</sup> polyoxygenated cyclohexanes (**3**)<sup>15</sup> and others.<sup>16,17</sup> An alternative method consists of  $\alpha$ -trimethylsilylation of acetaldehyde *t*-butylimine followed by deprotonation and reaction with a carbonyl compound (eq 5).<sup>17,18</sup>  $\alpha,\alpha$ -Disilylation is accomplished similarly and leads also via condensation with aldehydes to a wide range of (*E*)- $\alpha,\beta$ -unsaturated aldehydes (eq 6).<sup>19,20</sup> It should be pointed out also that directed aldol condensations between lithiated acetaldehyde imines and aldehydes or ketones have been frequently reported (eq 7).<sup>6,21</sup> Other electrophiles, e.g. nitriles,<sup>22,23</sup> carboxylic esters,<sup>6</sup> and enones,<sup>6,24</sup> lead to the expected reaction products.



Nitration can be accomplished after deprotonation and reaction with ethyl nitrate, but the reaction takes a partially different course with propyl nitrate (eq 8).<sup>25</sup> In a similar way,  $\beta$ -enamino and  $\beta$ -iminosulfoxides are obtained by using menthyl *p*-toluenesulfonate.<sup>26</sup> Lithiated acetaldehyde *t*-butylimine reacts with chlorophosphites to give  $\alpha$ -phosphorylated imines, which are in equilibrium with their enamino form.<sup>27,28</sup> Without the initial deprotonation step, *N*-phosphorylation takes place.<sup>29</sup>

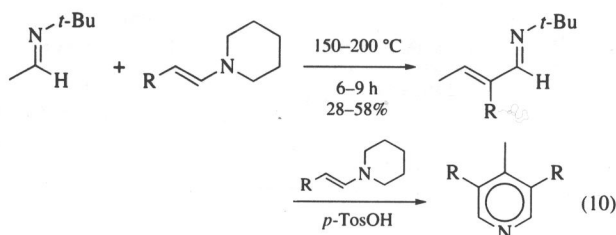


**$\alpha$ -Functionalization.** Acetaldehyde *t*-butylimine is  $\alpha,\alpha,\alpha$ -trichlorinated with *N*-Chlorosuccinimide at room temperature (eq 9).<sup>30</sup> The resulting chloral imine is a suitable substrate for conversion into  $\alpha,\alpha$ -dichloroacetimidates,  $\alpha$ -cyano- $\beta,\beta$ -dichloroenamines,  $\alpha,\beta,\beta$ -trisulfonylated enamines, and  $\beta,\beta,\beta$ -trichloroamines.<sup>30</sup> The reaction of acetaldehyde *t*-butylimine with aromatic nitroso compounds affords  $\alpha$ -(*N*-hydroxy-*N*-aryl)aminoaldehydes or  $\alpha$ -diimines.<sup>31,32</sup>

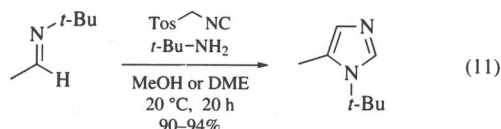


**Synthesis of Heterocycles.** Condensation of acetaldehyde *t*-butylimine with enamines at 150–220 °C affords rearranged 1-azabutadienes via cycloreversion of an azacyclobutene intermediate, formed by [2 + 2] cycloaddition of the reactants (eq 10).<sup>33</sup> Further reaction of the 1-azabutadienes with enamines in the presence of *p*-toluenesulfonic acid produces pyridines (eq 10).<sup>33</sup>

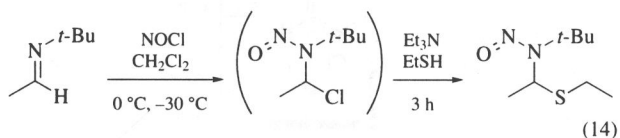
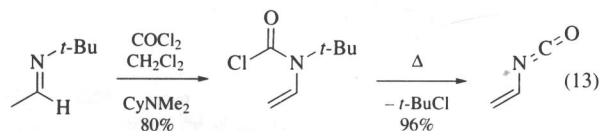
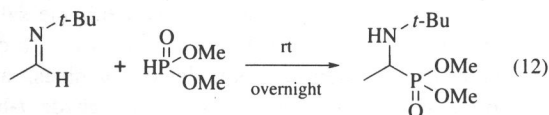
A very convenient synthesis of the imidazole nucleus consists of the reaction of acetaldehyde *t*-butylimine with *p*-Tolylsulfonylmethyl Isocyanide (TosMIC) in the presence of *t*-butylamine (eq 11).<sup>34</sup> The same aldimine is readily oxygenated by



peroxy acids to the corresponding oxaziridine.<sup>35-37</sup> Asymmetric oxidations have been performed with monoperoxykamphoric acid.<sup>35,36</sup>



**Reactions at the Imino Bond.** Nucleophilic addition of dimethyl phosphite across the imino bond of acetaldehyde *t*-butylimine without any solvent delivers the addition product (eq 12).<sup>38</sup> Functionalization at the nitrogen atom is accomplished with *Phosgene*, which gives the *N*-vinylcarbamoyl chloride (eq 13).<sup>39,40</sup> Upon thermolysis,  $\alpha,\beta$ -unsaturated isocyanates and *t*-butyl chloride are produced (eq 13).<sup>40</sup> Functionalized *N*-nitrosodialkylamines are accessible from acetaldehyde *t*-butylimine via reaction with *Nitrosyl Chloride* and, for example, *Ethanethiol* (eq 14).<sup>41</sup>



**Related Reagents.** Acetaldoxime; Acetone Cyclohexylimine; Acetone Hydrazone; 2-Chloro-2-methylpropanal *N*-Isopropylimine; 1-(*N,N*-Dimethylamino)-2-methyl-1-propene; Propionaldehyde *t*-Butylimine.

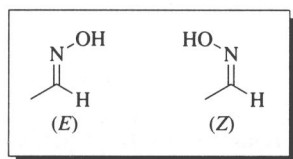
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## Acetaldoxime



[107-29-9]  $\text{C}_2\text{H}_5\text{NO}$  (MW 59.07)  
(E)  
[5780-37-0]  
(Z)  
[5775-72-4]

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

**Alternate Name:** acetaldehyde oxime.

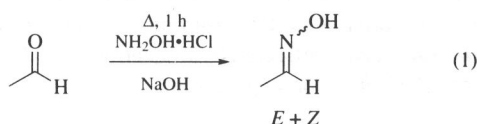
**Physical Data:** (E) and (Z) mixture bp 114–115 °C; mp 47 °C.

**Solubility:** sol most organic solvents, e.g. THF,  $\text{CHCl}_3$ , 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.<sup>2</sup>

**Analysis of Reagent Purity:**  $^1\text{H}$  NMR.

**Preparative Method:** reaction of freshly distilled **Acetaldehyde** with **Hydroxylamine** hydrochloride in the presence of a base (eq 1).<sup>3,11</sup>

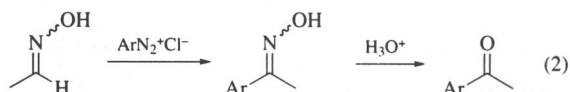


**Handling, Storage, and Precautions:** the oxime is preferably freshly prepared. The freshly prepared solid compound decomposes slowly on standing. Use in a fume hood.

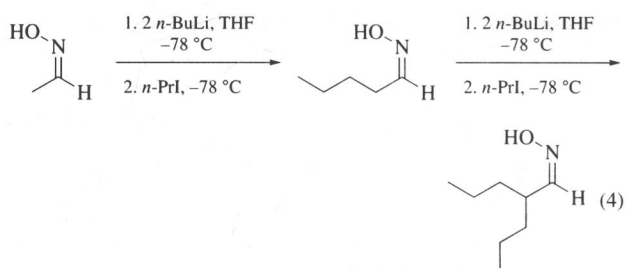
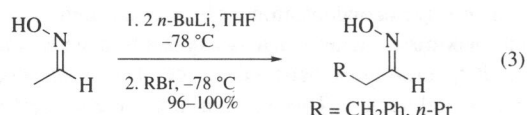
**Introduction.** Unsymmetrical oximes, like acetaldoxime, occur as a mixture of (E) and (Z) isomers across the carbon–nitrogen double bond (often referred to as *syn* and *anti* isomers, respectively). The position of the equilibrium changes with the conditions. A frequently reported equilibrium is situated around 40% (E) in the pure state and 46% (E) in aqueous acid,<sup>12</sup> but the position of the equilibrium is independent of the temperature and the concentration of the acid.<sup>13</sup> (Z)-Acetaldoxime can be prepared by slow crystallization of a freshly distilled mixture of

(E)/(Z) isomers.<sup>13</sup>  $^1\text{H}$  NMR<sup>11,14</sup> and  $^{13}\text{C}$  NMR<sup>15</sup> have been used to establish the (E)/(Z) configurations of oximes.

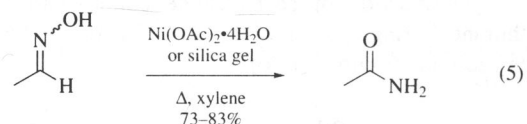
**Acetylation of Arenes via Diazonium Salts.** The reaction of acetaldoxime with aromatic diazonium salts affords oximes of acetophenones, which are hydrolyzed in acid medium to give aryl methyl ketones (eq 2).<sup>1</sup>



**$\alpha$ -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  $\alpha$ -alkylated (Z)-oximes (eqs 3 and 4).<sup>2</sup>  $\alpha,\alpha$ -Dialkylation by further alkylation in similar way has been achieved (eq 4).<sup>2</sup> It is generally known that ketone oximes can be deprotonated and alkylated regioselectively *syn* to the oxime hydroxy group.<sup>16,17</sup> It is essential to perform the deprotonation and alkylation at  $-78$  °C as otherwise no  $\alpha$ -alkylated oximes are isolated, the major byproducts being nitriles.<sup>16</sup>

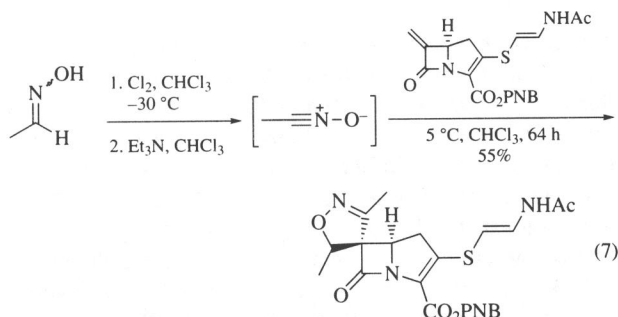
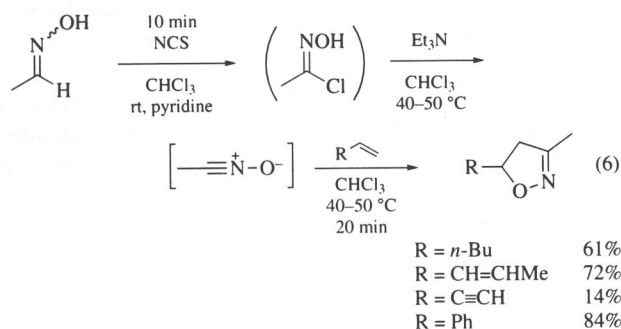


**Rearrangement into Acetamide.** Heating of acetaldoxime in xylene in the presence of 0.2 mol % **Nickel(II) Acetate**<sup>3</sup> or silica gel<sup>4</sup> as catalyst caused isomerization into acetamide (eq 5).

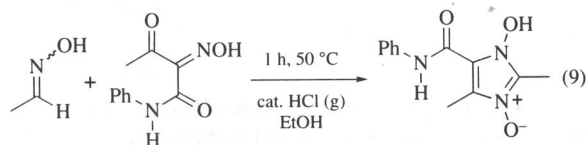
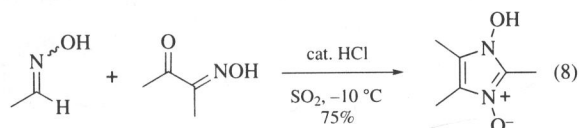


**Synthesis of Heterocycles.** Chlorination of acetaldoxime with *N*-Chlorosuccinimide<sup>5</sup> or **Chlorine** gas<sup>8,18</sup> in chloroform affords acetohydroxamic acid chloride, which suffers dehydrochlorination with **Triethylamine** to give **Acetonitrile N-Oxide**. The latter 1,3-dipole undergoes 1,3-dipolar cycloaddition to alkenes giving 2-isoxazolines in a one-pot procedure (eq 6).<sup>5</sup> 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).<sup>8</sup>





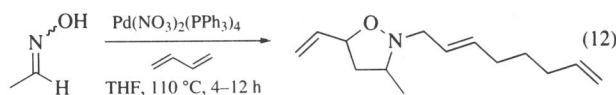
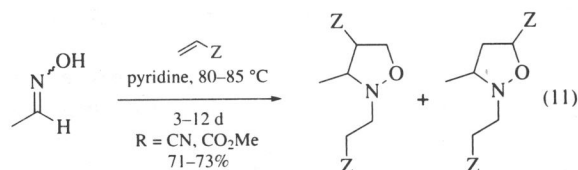
The cyclocondensation of acetaldoxime with biacetyl monooxime yields 1-hydroxy-2,4,5-trimethylimidazole 3-oxide,<sup>19</sup> originally believed to be 4-hydroxy-3,4,6-trimethyl-1,2,5-oxadiazine.<sup>20</sup> The reaction is preferably performed in liquid sulfur dioxide in the presence of catalytic amounts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



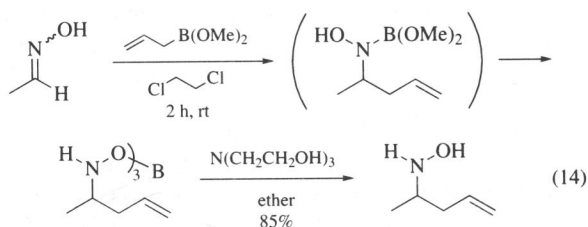
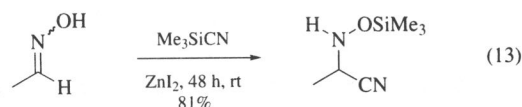
Upon reaction of acetaldehyde oxime with 2,2-dimethylthiirane, ring expansion to 3-hydroxy-2,5,5-trimethylthiazolidine occurs (eq 10).<sup>7</sup>



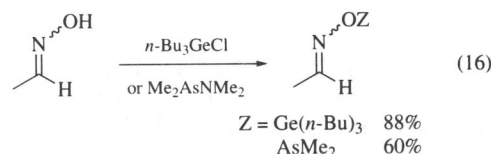
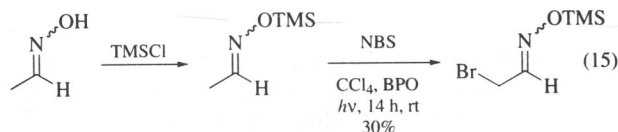
**1,3-Dipolar Cycloaddition.** Acetaldoxime cycloadds very slowly to *Methyl Acrylate* and *Acrylonitrile*, giving 2:1 adducts as mixtures of regioisomers and stereoisomers (eq 11).<sup>10</sup> The palladium-catalyzed cycloaddition of the reagent to 1,3-butadiene yields an isoxazolidine via the intermediacy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



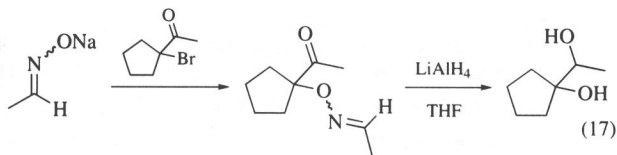
**Addition Reactions Across the Carbon–Nitrogen Double Bond.** *Cyanotrimethylsilane* adds to acetaldoxime to give the cyanated adduct (eq 13),<sup>22</sup> while allylboronates behave similarly to afford the adduct, which disproportionates and can subsequently be cleaved to the alkenic hydroxylamine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



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



**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.<sup>28</sup>



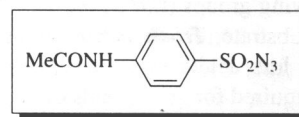
The reaction involves carbon radical addition to the carbon–nitrogen double bond.

**Related Reagents.** Acetaldehyde; Acetaldehyde *N*-*t*-Butylimine; Acetonitrile *N*-Oxide; Formaldoxime; Hydroxylamine.

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## p-Acetamidobenzenesulfonyl Azide



[2158-14-7]

C<sub>8</sub>H<sub>8</sub>N<sub>4</sub>O<sub>3</sub>S

(MW 240.24)

(reagent for diazo function transfer to activated methylene groups;<sup>1</sup> can functionalize double bonds by cycloaddition reactions<sup>9,10</sup>)

**Alternate Name:** *p*-ABSA.

**Physical Data:** mp 106–108 °C;<sup>1</sup> 112–114 °C.<sup>2</sup> Decomposition begins at about 120 °C in an open cup system.

**Solubility:** sol CH<sub>2</sub>Cl<sub>2</sub>; sparingly sol toluene; insol petroleum ether.

**Form Supplied in:** colorless or slightly brown crystals.

**Analysis of Reagent Purity:** <sup>1</sup>H NMR, IR, elemental analysis.

**Preparative Methods:** the title reagent can be prepared by nitrosation of *p*-acetamidobenzenesulfonyl hydrazide,<sup>2,3</sup> by reaction of *p*-acetamidobenzenesulfonyl chloride with **Sodium Azide** in acetone solution,<sup>1</sup> or more conveniently under phase transfer conditions with CH<sub>2</sub>Cl<sub>2</sub>/water in the presence of tetraethylammonium chloride<sup>1</sup> or with benzene/water in the presence of Aliquat 336 (99% yield at rt in 0.5 h).<sup>4</sup>

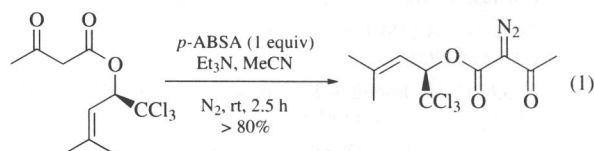
**Purification:** recrystallization from toluene.

**Handling, Storage, and Precautions:** relatively safe reagent and no special instructions for its storage and handling are mentioned in the literature. Proper caution should be used as with all azide reagents. Use in a fume hood.

**Diazo Transfer Reagent.** *p*-Acetamidobenzenesulfonyl azide offers some advantages in safety and ease of product separation and was recommended<sup>1,5</sup> as an alternative and substitute for the standard reagent, ***p*-Toluenesulfonyl Azide**,<sup>6</sup> in diazo transfer chemistry. The reaction times with *p*-ABSA are longer than with other azides.<sup>1a</sup>

Thus far, the reagent has only been employed in the direct transfer of a diazo function to methylene groups flanked by one or two carbonyls.

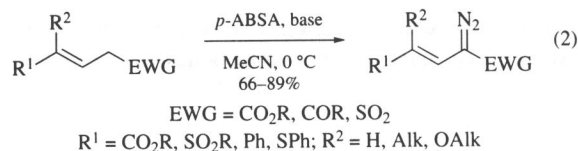
Well-known diazodicarbonyl compounds, including diazodimedone, diazoisopropylidenemalononic acid, diazomalonic, and diazoacetoacetic acid esters<sup>1</sup> as well as optically active esters of diazoacetoacetic acid (eq 1)<sup>5</sup> are readily available from *p*-ABSA and Et<sub>3</sub>N in good yields (72–95%).



In the presence of a stronger base (**Sodium Ethoxide** in ethanol) the *p*-acetamidobenzenesulfonyl amide of diazomalonic acid ethyl ester was obtained as the major product from diethyl malonate.<sup>3</sup>

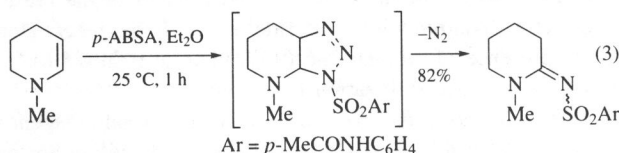
Avoid Skin Contact with All Reagents

*p*-ABSA also proves to be a versatile and effective reagent for the synthesis of various vinyl diazomethanes with one or two electron withdrawing groups (EWG) (eq 2).<sup>1,7,8</sup> When two EWG are in a parent substrate, *Triethylamine* is usually an effective base,<sup>1,7</sup> but with less acidic systems, *1,8-Diazabicyclo[5.4.0]undec-7-ene* is required for good yields of vinyl diazomethanes.<sup>8</sup> The presence of a vinyl group apparently enhances the transformation.<sup>1</sup>



Activation of a methylene by one carbonyl group as in dihydro-2-indolone, affords a relatively low yield of diazoidindolone (39%) with *p*-ABSA and Et<sub>3</sub>N as the base.<sup>1a</sup>

**Functionalization of Double Bonds.** Nucleophilic double bonds of indole, *N*-methylindole, and tetrahydropyridine readily add to the 1,3-dipole moiety of *p*-ABSA to give, as the final products, indolidylidene-<sup>9</sup> and piperidylidene-2-arylsulfonamides (eq 3)<sup>10</sup> in good yields.



**'Nitrogenic' Source.** Catalytic decomposition of *p*-ABSA by platinum(II) complexes,<sup>11</sup> thermolysis at fairly high temperatures (above 130–150 °C) in *o*- and *p*-xylenes, *N*,*N*-dimethylaniline,<sup>2</sup> or pyridine,<sup>2,12</sup> and reaction with triphenylstibine<sup>13</sup> gives rise to the formal insertion or addition products of *p*-acetamidobenzenesulfonylnitrene into the corresponding substrates in good to moderate yields.

**Related Reagents.** *p*-Dodecylbenzenesulfonyl Azide; Methanesulfonyl Azide; *p*-Toluenesulfonyl Azide.

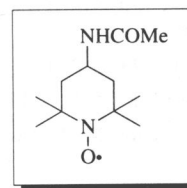
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## 4-Acetamido-2,2,6,6-tetramethyl-1-piperidinyloxyl<sup>1</sup>



[14691-89-5]

C<sub>11</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>

(MW 213.30)

(reagent and catalyst for selective oxidation of alcohols<sup>2</sup>)

**Alternate Names:** 4-acetamido-TEMPO; 4-acetylmino-TEMPO.

**Physical Data:** mp 146–147 °C,<sup>2</sup> 147.5 °C.<sup>3</sup>

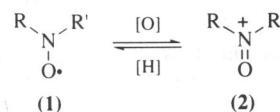
**Solubility:** nearly insol hexane, ether; sol ethanol, acetone, acetonitrile, methylene chloride; slightly sol water, from which it can be recrystallized.

**Form Supplied in:** red or pink solid, commercially available.

**Preparative Method:** can be easily prepared in high yield from 4-amino-2,2,6,6-tetramethylpiperidine.<sup>2</sup>

**Handling, Storage, and Precautions:** completely stable and nonhygroscopic.

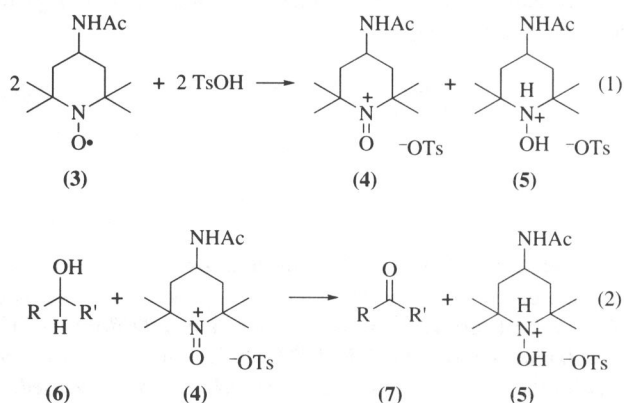
**Oxidation of Alcohols.** 4-Acetamido-TEMPO is a representative of the nitroxide radicals (1) which have been used as reagents or catalysts for the oxidation of organic compounds.<sup>1</sup> Several nitroxide radicals have been converted to the corresponding oxoammonium salts (2) and used as stoichiometric oxidizing reagents.<sup>1</sup> Nitroxide radicals have also been used as catalysts in the presence of a secondary, stoichiometric oxidant (see *2,2,6,6-Tetramethylpiperidin-1-oxyl*).<sup>1</sup>



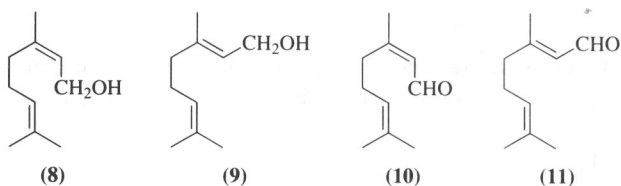
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4-Acetamido-TEMPO (**3**) is not, itself, a reagent for the oxidation of alcohols. Rather, it serves as a convenient precursor for the in situ preparation of an oxoammonium salt (**4**), which is the true oxidant. The oxoammonium salt (**4**) is the product of the acid-catalyzed disproportionation of (**3**) to (**4**) and (**5**) in the presence of *p*-Toluenesulfonic Acid (eq 1) and is a highly selective reagent for alcohol oxidation (eq 2).<sup>1</sup> The reactions are carried out in methylene chloride in which TsOH·H<sub>2</sub>O is essentially insoluble. The only products of the reaction are the desired carbonyl compound product (**7**) and the hydroxylamine salt (**5**), which is completely insoluble in methylene chloride. Product isolation simply involves the filtration of (**5**) and the evaporation of methylene chloride. Compound (**5**) can be converted back to the nitroxide radical (**3**) in quantitative yield.<sup>2</sup>



The reaction has been used for the oxidation of a variety of alcohols with excellent yields of isolated products.<sup>2</sup> Primary alcohols are converted to the corresponding aldehydes, and no over-oxidation is observed. Secondary alcohols react as well as primary alcohols and provide the corresponding ketones. The mildness of this reaction has been demonstrated by the oxidations of nerol (**8**) and geraniol (**9**) to the corresponding *cis*-citral (**10**) and *trans*-citral (**11**).



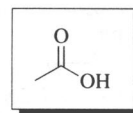
Oxidation with this reagent does not take place when there is an oxygen or nitrogen in the  $\beta$ -position to the alcohol being oxidized and does not take place with 1,2-diols or sugars. Amines,<sup>1,4</sup> thiols,<sup>5</sup> phenols,<sup>6</sup> indoles,<sup>7</sup> benzyl ethers,<sup>1</sup> and ketones (very slow)<sup>1</sup> react with oxoammonium salts and may interfere with alcohol oxidation. However, sulfides, most ethers, amides, esters, and double bonds do not react with oxoammonium salts and should not interfere.<sup>1</sup>

A number of other oxoammonium salts have been described in the literature.<sup>1</sup> In addition, TEMPO-type nitroxide radicals have been used as specific catalysts for the oxidation of alcohols using one or several secondary, stoichiometric oxidants.<sup>1,8</sup> Neither 4-acetamido-TEMPO nor any of its derivatives have been used in this manner, but they should function satisfactorily.

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## Acetic Acid<sup>1</sup>



[64-19-7]

C<sub>2</sub>H<sub>4</sub>O<sub>2</sub>

(MW 60.05)

(common organic reaction solvent; reagent for protonolysis of organometallic compounds,<sup>5,6</sup> synthesis of aromatic methyl ketones,<sup>10</sup> lactones,<sup>15</sup> heterocycles<sup>13</sup>)

Alternate Name: ethanoic acid.

Physical Data: weak organic acid,  $pK_a$  4.77;  $d_4^{20}$  1.049 g cm<sup>-3</sup>; mp 14.7 °C; bp 118 °C (30 °C/31 mmHg). Forms azeotropes with many common solvents, such as benzene, pyridine, DMF, and dioxane.

Solubility: miscible with water, ethanol, acetone, benzene, ether, and carbon tetrachloride; insol CS<sub>2</sub>.

Form Supplied in: widely available as glacial acetic acid, >98% purity.

Analysis of Reagent Purity: analyzed by titration with base.<sup>2,18</sup>

High purity grades of acetic acid (>99%) are determined by the freeze-point method. Formic acid content can be determined by a redox titration based on oxidation with lead tetraacetate. Methods for analysis of trace impurities such as water, iron, or chlorine are known.

Purification: among many methods, distillation over traces of oxidants in the presence of Ac<sub>2</sub>O is effective.<sup>19</sup>

Handling, Storage, and Precautions: acetic acid is flammable with a flash point of 40 °C.<sup>3</sup> This hazard is often overlooked by the practicing chemist and has been the source of laboratory accidents. Acetic acid is a corrosive material. Basic safety equipment including eye protection, gloves, and a chemical apron should be worn during all operations with acetic acid. Vapors will cause intense irritation to mouth, nose, eyes, skin, and upper respiratory tract. Use of an appro-

Avoid Skin Contact with All Reagents