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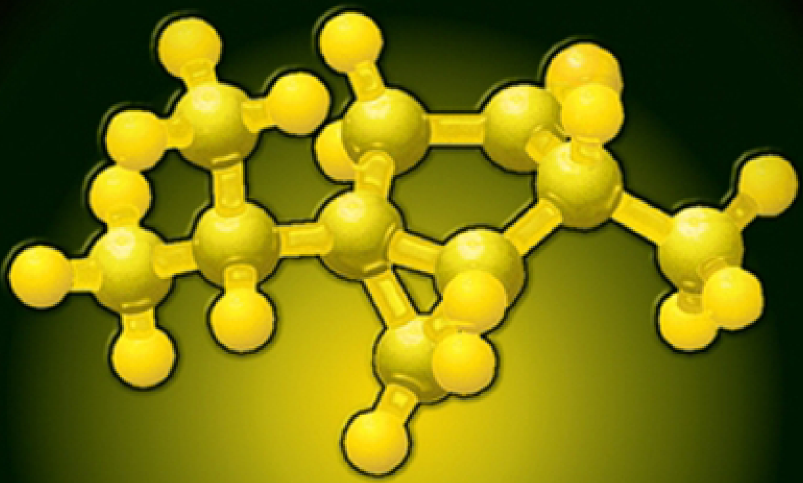

# Handbook of Reagents for Organic Synthesis

## Reagents for Radical and Radical Ion Chemistry

*Edited by*
**David Crich**

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# *Handbook of Reagents for Organic Synthesis*

# *Reagents for Radical and Radical Ion Chemistry*

Edited by

**David Crich**
*Wayne State University, Detroit, MI, USA*

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# Contents

**General Abbreviations**

# Preface

As stated in its Preface, the major motivation for our undertaking publication of the *Encyclopedia of Reagents for Organic Synthesis* was 'to incorporate into a single work a genuinely authoritative and systematic description of the utility of all reagents used in organic chemistry.' By all accounts, this reference compendium succeeded admirably in approaching this objective. Experts from around the globe contributed many relevant facts that define the various uses characteristic of each reagent. The choice of a masthead format for providing relevant information about each entry, the highlighting of key transformations with illustrative equations, and the incorporation of detailed indexes serve in tandem to facilitate the retrieval of desired information.

Notwithstanding these accomplishments, the editors came to recognize that the large size of this eight-volume work and its cost of purchase often deterred the placement of copies of the *Encyclopedia* in or near laboratories where the need for this type of information is most critical. In an effort to meet this demand in a cost-effective manner, the decision was made to cull from the major work that information having the highest probability for repeated consultation and to incorporate the same into a set of handbooks. The latter would also be purchasable on a single unit basis.

The ultimate result of these deliberations was the publication of the *Handbook of Reagents for Organic Synthesis,* the first four volumes of which were published 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

Since then, the fifth, sixth, seventh, eighth, ninth and tenth members of this series listed below have made their appearance:

*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*
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*Catalyst Components for Coupling Reactions*
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Each of the volumes contain a selected compilation of those entries from the original *Encyclopedia* that bear on the specific topic. The coverage of the last six handbooks also extends to the electronic sequel *e-EROS*. Ample listings can be found to functionally related reagents contained in the original work. For the sake of current awareness, references to recent reviews and monographs have been included, as have relevant new procedures from *Organic Syntheses*.

The present volume entitled *Reagents for Radical and Radical Ion Chemistry* constitutes the eleventh entry in a continuing series of utilitarian reference works. As with its predecessors, this handbook is intended to be an affordable, enlightening compilation that will hopefully find its way into the laboratories of all practicing synthetic chemists. Every attempt has been made to be of the broadest possible relevance and it is hoped that our many colleagues will share in this opinion.

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# Introduction

In the hands of the cognoscenti, radicals and their charged counterparts, the radical ions have long left behind their image as highly reactive uncontrollable intermediates unsuitable for application in fine chemical synthesis. Nowhere is this more apparent than in the area of stereoselective radical reactions that, as recently as the mid 1980s, were considered nothing more than a pipe dream, but that, with improved methods for radical generation, rapidly evolved within the space of a few years sufficiently to warrant publication of dedicated review articles and books. Indeed, the stereoselectivity of well-planned radical reactions is now such that it can equal and even surpass that of more widely appreciated two-electron systems. Unfortunately, it remains the case that most undergraduate organic chemistry textbooks still introduce budding chemists to radical reactions through the chlorination of methane, and so convey the general impression of a complex and unselective chemistry. Against this background, it is hoped that the reagents collected in this handbook will serve to illustrate the variety of transformations that may be readily achieved through radical and radical ion chemistry and help at least a proportion of practicing organic chemists overcome whatever remaining reluctance they may have to the application of radical chemistry in their synthetic schemes.

The success of modern radical chemistry has been achieved at the hands of numerous practitioners of the art whose dedication has resulted in the development of many of the reagents featured here. However, it is important to acknowledge that modern radical chemistry is built on a very extensive physical organic foundation and on the pioneering work of many individuals when the field was much less popular than today. Accordingly, it is fitting and appropriate that the list of selected monographs and review articles with which this handbook opens begins with a section on general and physical organic aspects before moving onto the chemistry of radical anions, then radial cations, and finally neutral radicals. Some of the monographs and reviews selected for these lists can no longer be considered recent, nevertheless they remain veritable treasure troves of little known underexploited processes waiting to be rediscovered and developed and it is for this reason that they are included here. The unbalanced division of the material, both in the lists of monographs and reviews and in the reagents themselves, with a heavy emphasis on the chemistry of neutral radicals, generally reflects the state of the art with respect to current applications in synthesis. It is to be hoped that this imbalance will be redressed as improved methods for the controlled generation of radical anions and cations become available.

Of the reagents featured in this volume, approximately one third are taken from the *Encyclopedia of Reagents for Organic Synthesis (EROS)*, published in 1995. Many of these are classical reagents in the field whose principal use has not changed in the intervening period. The remainder, and indeed the bulk, of the entries are divided approximately equally between completely new articles and updated versions of original *EROS* articles taking into account recent developments, written by experts in the field for the continually expanding online encyclopedia *(e-EROS)*. The main sequence of reagents in this volume is alphabetical in keeping with the *EROS* and *e-EROS* format.

It is hoped that this handbook will serve as a useful resource to synthetic chemists and to stimulate the ever wider use of radical and radical ions in synthetic organic chemistry.

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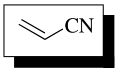
# A

## Acrylonitrile



*[107-13-1]* $C_3H_3N$ (MW 53.06)

(electrophile in 1,4-addition reactions; radical acceptor; dienophile; acceptor in cycloaddition reactions)

*Physical Data:* mp −83 °C; bp 77 °C; $d$ 0.806 g cm$^{-3}$; $n_D$ 1.3911.

*Solubility:* miscible with most organic solvents; 7.3 g of acrylonitrile dissolves in 100 g of water at 20 °C.

*Form Supplied in:* colorless liquid (inhibited with 35–45 ppm hydroquinone monomethyl ether); widely available.

*Purification:* the stabilizer can be removed prior to use by passing the liquid through a column of activated alumina or by washing with a 1% aqueous solution of NaOH (if traces of water are allowed in the final product) followed by distillation. For dry acrylonitrile, the following procedure is recommended. Wash with dilute $H_2SO_4$ or $H_3PO_4$, then with dilute aqueous $Na_2CO_3$ and water. Dry over $Na_2SO_4$, $CaCl_2$, or by shaking with molecular sieves. Finally, fractional distillation under nitrogen (boiling fraction of 75–75.5 °C) provides acrylonitrile which can be stabilized by adding 10 ppm *t*-butyl catechol or hydroquinone monomethyl ether. Pure acrylonitrile is distilled as required.**[1a]**

*Handling, Storage, and Precautions:* explosive, flammable, and toxic liquid. May polymerize spontaneously, particularly in the absence of oxygen or on exposure to visible light, if no inhibitor is present. Polymerizes violently in the presence of concentrated alkali. Highly toxic through cyanide effect. Use in a fume hood.

## Original Commentary

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*University of Toronto, Toronto, Ontario, Canada*

**Deuterioacrylonitrile.** Deuterium-labeled acrylonitrile can be obtained by reduction of propiolamide-$d_3$ with lithium aluminum hydride, followed by $D_2O$ workup. The resulting acrylamide can then be dehydrated with $P_2O_5$.**[1b]**

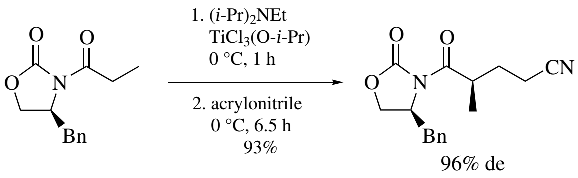
**Reactions of the Nitrile Group.** Various functional group transformations have been carried out on the nitrile group in acrylonitrile. Hydration with concentrated sulfuric acid at 100 °C yields acrylamide after neutralization.**[2]** Secondary and tertiary alcohols produce *N*-substituted acrylamides under these conditions in excellent yield (Ritter reaction).**[3]** Heating in the presence of dilute sulfuric acid or with an aqueous basic solution yields acrylic acid.**[4]** Imido ethers have been prepared by reacting acrylonitrile with alcohols in the presence of anhydrous hydrogen halides.**[5]** Anhydrous formaldehyde reacts with acrylonitrile in the presence of concentrated sulfuric acid to produce 1,3,5-triacrylylhexahydrotriazine.**[6]**

**Reactions of the Alkene.** Reduction with hydrogen in the presence of Cu,**[7]** Rh,**[8]** Ni,**[9]** or Pd**[10]** yields propionitrile. Acrylonitrile can be halogenated at low temperature to produce 2,3-dihalopropionitriles. For example, reaction with bromine leads to dibromopropionitrile in 65% yield.**[11]** Also, treatment of acrylonitrile with an aqueous solution of hypochlorous acid, gives 2-chloro-3-hydroxypropionitrile in 60% yield.**[12]** $\alpha$-Oximation of acrylonitrile has been achieved using Co$^{II}$ catalysts, *n*-butyl nitrite and phenylsilane.**[13]**

**Nucleophilic Additions.** A wide variety of nucleophiles react with acrylonitrile in 1,4-addition reactions. These Michael-type additions are often referred to as cyanoethylation reactions.**[14]** The following list illustrates the variety of substrates which will undergo cyanoethylation: ammonia, primary and secondary amines, hydroxylamine, enamines, amides, lactams, imides, hydrazine, water, various alcohols, phenols, oximes, sulfides, inorganic acids like HCN, HCl, HBr, chloroform, bromoform, aldehydes, and ketones bearing an $\alpha$-hydrogen, malonic ester derivatives, and other diactivated methylene compounds.**[15]** Stabilized carbanions derived from cyclopentadiene and fluorene and 1–5% of an alkaline catalyst also undergo cyanoethylation. The strongly basic quaternary ammonium hydroxides, such as benzyltrimethylammonium hydroxide (Triton B), are particularly effective at promoting cyanoethylation because of their solubility in organic media. Reaction temperatures vary from −20 °C for reactive substrates, to heating at 100 °C for more sluggish nucleophiles. The 1,4-addition of amines has recently been used in the synthesis of poly(propyleneimine) dendrimers.**[16]**

Phosphine nucleophiles have been reported to promote nucleophilic polymerization of acrylonitrile.**[17]**

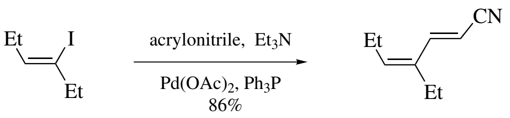
Addition of organometallic reagents to acrylonitrile is less efficient than to conjugated enones. Grignard reagents react with acrylonitrile by 1,2-addition and, after hydrolysis, give $\alpha,\beta$-unsaturated ketones.**[18]** Lithium dialkylcuprate ($R_2CuLi$) addition in the presence of chlorotrimethylsilane leads to double addition at the alkene and nitrile, giving a dialkyl ketone.**[19]** Yields of only 23–46% are obtained in the conjugate addition of *n*-BuCu·$BF_3$ to acrylonitrile.**[20]** An enantioselective Michael reaction has been achieved with titanium enolates derived from *N*-propionyloxazolidone (eq 1).**[21]**



(1)

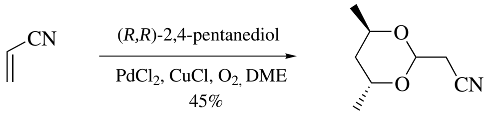
Acrylonitrile fails to react with trialkylboranes in the absence of oxygen or other radical initiatiors. However, secondary trialkylboranes transfer alkyl groups in good yield when oxygen is slowly bubbled through the reaction mixture.**[22]** Primary and secondary alkyl groups can be added in excellent yields using copper(I) methyltrialkylborates.[23] Reaction of acrylonitrile with an organotetracarbonylferrate in a conjugate fashion provides 4-oxonitriles in moderate (25%) yields.[24]

**Transition Metal-catalyzed Additions.** Palladium-catalyzed Heck arylation and alkenylation occurs readily with acrylonitrile (eq 2).[25] Double Heck arylation is observed in the $Pd^{II}$/montmorillonite-catalyzed reaction of aryl iodides with acrylonitrile.[26]



(2)

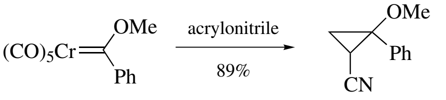
$Pd^{II}$ catalyzed oxidation of the double bond in acrylonitrile in the presence of an alcohol (Wacker-type reaction) produces an acetal in high yield.[27] When an enantiomerically pure diol such as (2*R*,4*R*)-2,4-pentanediol is used, the corresponding chiral cyclic acetal is produced (eq 3).[28]



(3)

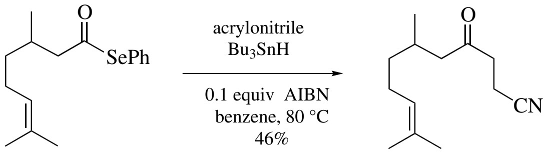
Hydrosilation[29a] of acrylonitrile with $MeCl_2SiH$ catalyzed by nickel gives the $\alpha$-silyl adduct. The $\beta$-silyl adduct is obtained when copper(I) oxide is used.[29b] The regioselectivity of the cobalt catalyzed hydrocarboxylation to give either the 2- or 3-cyanopropionates can also be controlled by the choice of reaction conditions.[30] Hydroformylation of acrylonitrile has also been described.[31]

Cyclopropanation of the double bond has been achieved upon treatment with a $Cu^I$ oxide/isocyanide or $Cu^0$/isocyanide complex. Although yields are low to moderate, functionalized cyclopropanes are obtained.[32,33] Photolysis of hydrazone derivatives of glucose in the presence of acrylonitrile provides the cyclopropanes in good yield, but with little stereoselectivity.[34] Chromium-based Fischer carbenes also react with electron deficient alkenes including acrylonitrile to give functionalized cyclopropanes (eq 4).[35]



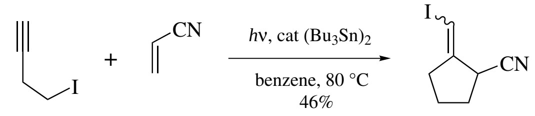
(4)

**Radical Additions.** Carbon-centered radicals add efficiently and regioselectively to the $\beta$-position of acrylonitrile, forming a new carbon–carbon bond.[36,37] Such radicals can be generated from an alkyl halide (using a catalytic amount of tri-*n*-butylstannane, alcohol (via the thiocarbonyl/$Bu_3SnH$), tertiary nitro compound (using $Bu_3SnH$), or an organomercurial (using $NaBH_4$). The stereochemistry of the reaction has been examined in cyclohexanes and cyclopentanes bearing an $\alpha$-stereocenter.[36] $Cr^{II}$ complexes, vitamin $B_{12}$, and a Zn/Cu couple have been shown to mediate the intermolecular addition of primary, secondary, and tertiary alkyl halides to acrylonitrile.[38] Acyl radicals derived from phenyl selenoesters and $Bu_3SnH$ also give addition products with acrylonitrile (eq 5).[39]



(5)

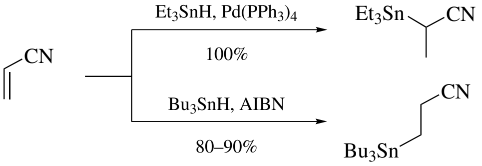
Radical additions with acrylonitrile have been used to prepare *C*-glycosides[36,37b] and in annulation procedures.[37c] Acrylonitrile has also been used in a [3 + 2] annulation based on sequential radical additions (eq 6).[40]



(6)

Alkyl and acyl $Co^{III}$ complexes add to acrylonitrile and then undergo $\beta$-elimination to give a product corresponding to vinylic C–H substitution.[41] This methodology is complementary to the Heck reaction of aryl and vinyl halides, which fails for alkyl and acyl compounds.[25]

Radicals other than those based on carbon also add to acrylonitrile. Heating acrylonitrile and tributyltin hydride in a 2:3 molar ratio in the presence of a catalytic amount of azobisisobutyronitrile yields exclusively the $\beta$-stannylated adduct in excellent yield.[42] Hydrostannylation in the presence of a $Pd^0$ catalyst gives only the $\alpha$-adduct (eq 7).[42c]



(7)

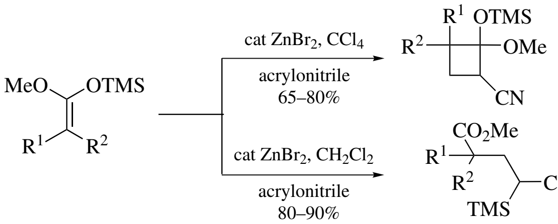
Treatment of ethyl propiolate with $Bu_3SnH$ in the presence of acrylonitrile results in addition of a tin radical to the $\beta$-site of the alkyne followed by addition to acrylonitrile. Use of excess acrylonitrile results in trapping of the radical followed by an annulation reaction, providing trisubstituted cyclohexenes.[43]

Thioselenation of the alkene using diphenyl disulfide, diphenyl diselenide, and photolysis gives the $\alpha$-seleno-$\beta$-sulfide in 75% yield by a radical addition mechanism.[44] Similarly, tris(trimethylsilyl)silane adds to acrylonitrile at 80–90 °C using AIBN to give the $\beta$-silyl adduct in 85% yield.[45]

**Pericyclic Reactions.** In the presence of a suitable alkene, the double bond in acrylonitrile undergoes a thermally induced ene reaction in low to moderate yield. For example, when (+)-limonene and acrylonitrile are heated in a sealed tube, the corresponding ene adduct is produced in 25% yield.[46]

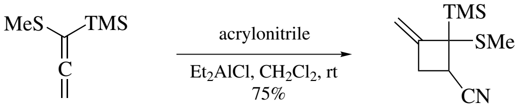
The thermal [2 + 2] dimerization of acrylonitrile has been known for many years. Good regioselectivity is observed but the yield is low and a mixture of stereoisomers is produced.[47] *Cis*-1,2-dideuterioacrylonitrile was used in this reaction to study the stereochemical outcome of the cycloaddition. It was concluded that a diradical intermediate was involved.[1b]

Other [2 + 2] reactions have been reported. Regioselective cycloaddition between a silyl enol ether and acrylonitrile yields a cyclobutane in the presence of light and a triplet sensitizer.[48a] Reaction between acrylonitrile and a ketene silyl acetal in the presence of a Lewis acid gives either substituted cyclobutanes or $\gamma$-cyanoesters depending on the Lewis acid and solvent (eq 8).[48c]



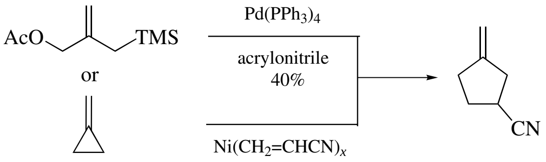
(8)

Dihydropyridines undergo stereoselective cycloaddition with acrylonitrile under photolytic conditions.[48c] The combination of a Lewis acid (zinc chloride) and photolysis promotes cycloaddition between benzene and acrylonitrile.[48d] Allenyl sulfides undergo Lewis acid catalyzed [2 + 2] cycloaddition with electron deficient alkenes including acrylonitrile with good regioselectivity but little stereoselectivity (eq 9).[49]



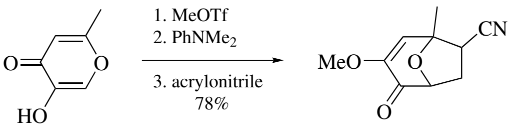
(9)

Metal catalysts promote [3 + 2] cycloaddition reactions with acrylonitrile, leading to carbocyclic compounds. Reaction of acrylonitrile with a trimethylenemethane (TMM) precursor in the presence of $Pd^0$ provides an efficient route to methylenecyclopentanes in moderate yield (40%).[50] A similar yield is obtained when a $Ni^0$ or $Pd^0$ catalyzed cycloaddition is employed starting from methylenecyclopropane.[51] Moreover, a variety of substituted methylenecyclopropanes have also been used to furnish substituted methylenecyclopentanes (eq 10).[51b]



(10)

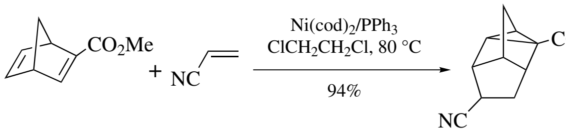
Five-membered heterocycles can be prepared from acrylonitrile by dipolar cycloadditions. Acrylonitrile undergoes efficient cycloaddition with 1,3-dipolar species[52] including nitrile oxides, nitrones, azomethine ylides, azides, and diazo compounds.[53] Cycloaddition of acrylonitrile with an oxopyrilium ylide generates stereoisomeric oxabicyclic compounds with excellent regioselectivity (eq 11).[54]



(11)

The dipolar cycloaddition of acrylonitrile with a hydroxypyridinium bromide is also highly regioselective.[55]

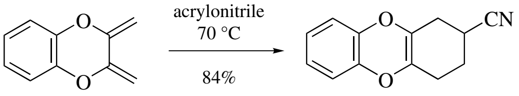
The [2 + 2 + 2] homo Diels–Alder cycloaddition between acrylonitrile and norbornadiene, substituted norbornadienes, or quadricyclane, has also been described under thermal and metal catalyzed conditions.[56] The effect of ligands and substituents on the stereo- and regioselectivity of the nickel catalyzed process has been investigated (eq 12).[56c,d]



(12)

Cobalt catalysts (octacarbonyldicobalt) also promote the cycloaddition of 1,6-diynes with acrylonitrile, yielding cyclohexadienes which are readily aromatized.[57]

Diels–Alder reactions using acrylonitrile have been widely reported with many different dienes. These include alkyl, aryl, alkoxy, alkoxycarbonyl, amido, phenylseleno, phenylthio, and alkoxyboranato substituted butadienes.[58] Reactions between acrylonitrile and furans, thiophenes, and thiopyrans have been reported. In some instances, Lewis acids accelerate the reaction.[59] Heterodienes including 2-azabutadienes and the 4-(oxa, aza, and thio) derivatives also undergo cycloaddition. Reactive dienes such as *o*-quinodimethanes,[60] benzofurans,[61] and dimethylbenzodioxanes react efficiently with acrylonitrile (eq 13).[62]



(13)

# First Update

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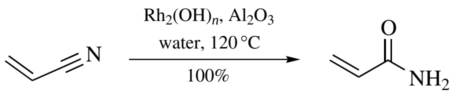
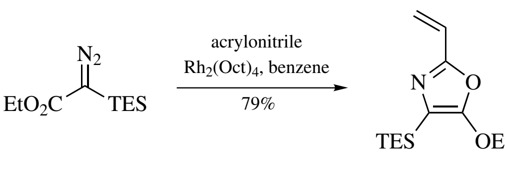
*Peakdale Molecular, Chapel-en-le-Frith, UK*

**Reactions of the Nitrile Group.** Although the majority of acrylonitrile reactivity involves the alkene moiety, there are several functional group conversions the nitrile can undergo. Various well-established methods exist for the hydrolysis of acrylonitrile to either acrylamide or acrylic acid. Recent additions include the high-yielding hydrolysis of acrylonitrile to acrylamide using alumina supported $Rh(OH)_n$ and water (eq 14).[63] The same transformation can be carried out using a colloid containing particles of Cu/Pd.[64]



(14)

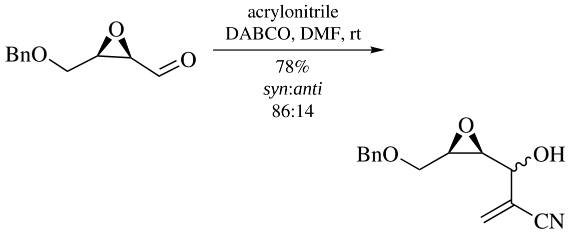
Oxazoles can be formed by exposing acrylonitrile to stabilized diazo compounds. The diazo ketone derived from acetophenone will react with acrylonitrile in good yield to furnish an oxazole; in this example $AlCl_3$ is used as the catalyst.[65] When decomposed with dirhodium tetraoctanoate in the presence of acrylonitrile, triethylsilylethyl diazoacetate affords a trisbsubstituted oxazole (eq 15).[66]



(15)

**Reactions of the Alkene.** A variety of metal catalysts will promote the reduction of acrylonitrile to propionitrile with molecular hydrogen. A metal free transfer hydrogenation protocol has been developed utilizing hydrazine and iodobenzene diacetate.[67] There are examples of acrylonitrile being epoxidized using *t*-BuOOH and chromium silicates.[68] Acrylonitrile can also be efficiently dihydroxylated using hydrogen peroxide and an iron catalyst [(6-$Me_3$-TPA)Fe($OTf)_2$].[69]

**Nucleophilic Additions.** Acrylonitrile is a very useful synthetic building block. It can be used to insert a three carbon chain featuring a nitrile which in turn can be functionalized in many ways. A large variety of nucleophiles will take part in Michael-type additions to acrylonitrile. Generally, a base such as Triton B is used, although there are instances where Lewis acids have been used in aqueous media with considerable success.[70] Tertiary amines such as DABCO will add to acrylonitrile, the intermediates formed from such reactions can go on to react with aldehydes (Bayliss–Hillman reaction).[71] Phosphorus bases can also be used for this purpose; however, reaction yields are modest.[72] Diastereoselective variants of the Bayliss–Hillman have been reported using substrates with delicate functionalities (eq 16).

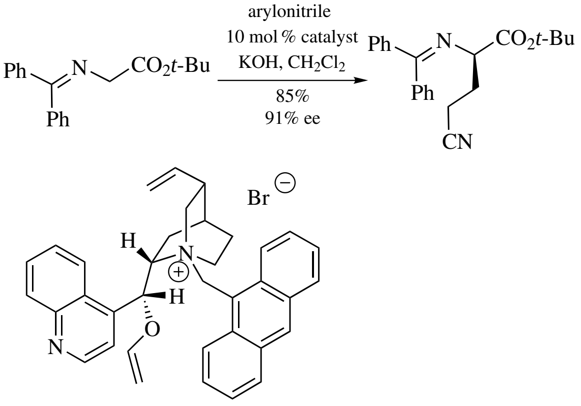


(16)

Inorganic acids such as HCl, HBr, and HI will react with acrylonitrile to form the relevant 3-halopropionitriles. A slightly milder alternative is the combination of TMSCl and wet MeCN.[73]

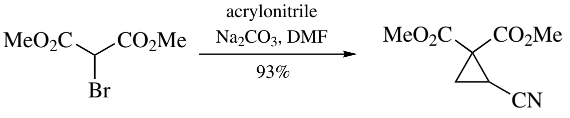
Perhaps the most synthetically useful reactions in this manifold are those of carbon-based nucleophiles such as enolates and malonates. Cyanoethylations of this type can proceed in a highly diastereoselective manner if a suitable chiral substrate is used. This strategy has been elegantly exploited in the total synthesis of clavolonine.[74] Recently, the use of bicyclic guanidine bases has been reported for the reaction of $\beta$-ketoesters with acrylonitrile.[75] Enolates generated from chiral *N*-propionoyloxazolidinone, a tertiary amine base, and a Lewis acid will add to acrylonitrile generating enantioenriched products upon cleavage of the auxiliary. Chiral imine controlled diastereoselective cyanoethylations have also been reported.[76] There are limited examples of enantioselective cyanoethylation processes. The benzophenone imine protected glycine derivatives can be cyanoethylated enantioselectively in high enantiomer excess using a cinchona alkaloid derived tertiary amine salt as the catalyst (eq 17).[77]

Acrylonitrile can act as the electrophile in the Stetter reaction. Upon treating a simple aldehyde with acrylonitrile in the presence of a modified thiazolium bromide, the corresponding $\gamma$-cyanoketone is generated in serviceable yield.[78] Electron-deficient alkenes such as acrylonitrile can be converted to substituted cyclopropanes in excellent yield using $\alpha$-bromocarbonyl compounds and a suitable base (eq 18).[79]



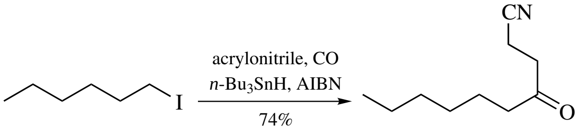
(17)

catalyst



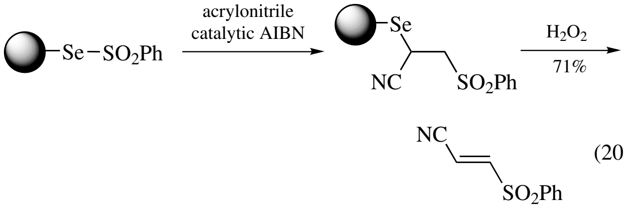
(18)

**Radical Additions.** The addition of carbon-centred radicals to the $\beta$-position of acrylonitrile complements the cyanoethylation of carbon-based nucleophiles in that no neighboring electron-withdrawing group is required to enable the C–C bond formation. Reaction yields and levels of regioselectivity are usually high. Conventionally, tri-*n*-$Bu_3SnH$ is used in concert with AIBN to initiate and propagate the radical reactions. Acyl carbamates can be converted to the corresponding acyl radicals using $SmI_2$; trapping with acrylonitrile generates $\gamma$-cyano ketones in good yield.[80] Similar products can be formed by the carbonylative addition of alkyl radicals to acrylonitrile (eq 19).[81]



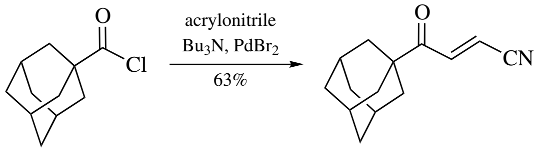
(19)

The S–H bond within $Ph_2PSH$ can be cleaved homolytically with $BEt_3$ and $O_2$. The sulfur-based radical formed will react readily with acrylonitrile to form the corresponding alkyl(diphenyl) phosphine sulfide in excellent yield.[82] The use of polymer-supported reagents in organic synthesis continues to grow. The sulfonyl radical formed by the action of AIBN on polystyrene-supported selenosulfonate will add to acrylonitrile to form the “trapped” polymer-bound addition product. On treatment with $H_2O_2$ the addition product is released oxidatively to form the vinyl sulfonate almost exclusively as the *E*-isomer (eq 20).[83]



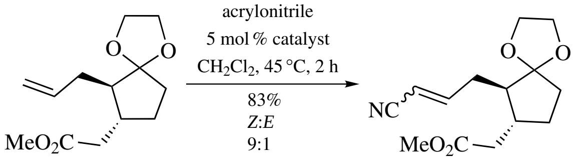
(20)

**Transition-metal-catalyzed additions.** Acrylonitrile has been used extensively in Heck reactions. It can be coupled readily to vinyl and aryl halides. Frequently $Pd(OAc)_2$ is used as the source of palladium; a tertiary amine base and elevated temperatures are required. There are also examples of aryl stannanes,[84] aryl silanols,[85] aryl boronic acids,[86] aryl tellurium iodides,[87] and aryl mercury chlorides[88] being used in Heck-type reactions with acrylonitrile. It is of note that Heck reactions involving acrylonitrile often give a mixture of alkene isomers.[89] In recent times efforts have been made to develop milder conditions for the Heck reaction. Alternative aryl donors such as aroyl chlorides will couple (decarboxylatively) with acrylonitrile without the need for a base. In this system $PdCl_2(PhCN)_2$ is used as catalyst in conjunction with a phase transfer agent $Bu_3BnNCl$.[90] Aryl diazonium salts can also be used as coupling partners, using a palladium imidazolium catalyst. Under these conditions the Heck coupling can be carried out at room temperature and without a base, though the yields are modest.[91] Tertiary alkanoyl chlorides such as adamantoyl chloride can be cross coupled with acrylonitrile to form $\gamma$-cyanoenones (eq 21).[92] An oxygen-promoted palladium-catalyzed Heck reaction has been developed. Hexenyl boronate esters and acrylonitrile will couple efficiently without the need for phosphine ligands using $Pd(OAc)_2$, $Na_2CO_3$, and molecular oxygen.[93]



(21)

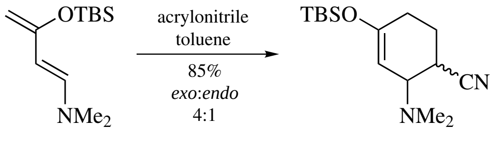
Olefin cross metathesis has developed rapidly over the last decade and is now a powerful synthetic methodology. Acrylonitrile will undergo cross metathesis with a range of electron-rich alkenes when Schrock's molybdenum alkylidene catalyst is employed.[94] As is the case in the majority of cross-metathesis chemistry, a mixture of *E*- and *Z*-alkene isomers is obtained. Under standard conditions, acrylonitrile is particularly a poor cross substrate for metathesis using the first generation ruthenium alkylidine catalyst developed by Grubbs.[95] The ether tethered phosphine free ruthenium alkylidene developed by Hoveyda, however, is adept at inducing the cross-metathesis reaction of acrylonitrile even with relatively complex olefins (eq 22).[96]



(22)

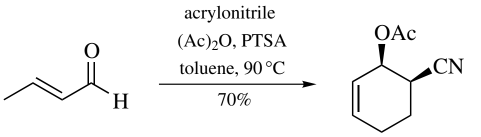
Modified versions of Hoveyda's catalyst have been shown to outperform the parent tethered runthenium alkylidine with simple substrates.[97] A polymer-supported version has also been reported.[98] More recently, a tailored ruthenium-based catalyst featuring bromopyridine ligands (in place of tricyclohexyl phosphines) was developed specifically for the cross metathesis of acrylonitrile.[96] The activity of this catalyst is comparable with Hoveyda's tethered ruthenium alkylidene. Although it was thought that only ruthenium alkylidenes without phosphine ligands could bring about acylonitrile cross metathesis, it transpires that good yields can be obtained if Grubbs' first generation catalyst is used with Cu(I) salts.[99] Chromium carbenoids will react with acrylonitrile to form cyclopropanes with electron-rich substituents.[100] This methodology complements the $\alpha$-halocarbonyl approach which produces cyanocyclopropanes with electron-withdrawing substituents.

**Pericyclic Reactions.** As an electron-deficient alkene, acrylonitrile will take part in Diels–Alder reactions with several types of dienes. Dienes with two activating group are particularly reactive and will react with acrylonitrile at room temperature in excellent yield.[101] Intriguingly in the example shown below the major product is the *exo*-adduct. This is in stark contrast to the reaction of acrylonitrile with methoxy butadiene which gives predominantly the *endo*-isomer.[102] In both cases the regioselectivity is very high (eq 23).



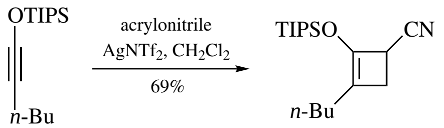
(23)

The reaction between cyclopentadiene and acrylonitrile has been studied at length. The process proceeds in high yield at ambient temperature.[103] In the presence of $Bi(OTf)_3$ furan reacts with acrylonitrile with alacrity.[104] Thiophene is a more recalcitrant substrate and yields are poor even at elevated temperatures and pressures.[105] When complexed to tris(pyrazolo)boratetungsten, 2,6-lutidine will function as a dieneophile in Diels–Alder reactions with acrylonitrile to yield highly functionalized cycloadducts after oxidative decomplexation.[106] When PhNCO is mixed with crotonaldehyde in conjunction with catalytic quantities of PTSA acid, the diene formed is trapped in situ by acrylonitrile furnishing aminocyanocylohexenes in reasonable yield and with excellent levels of diastereoselectivity.[107] The analogous reaction can be carried out with acetic anhydride in the place of PhNCO to provide alkoxy carbonyl cyano cyclohexenes which can be hydrolyzed enzymatically to form enantiopure cyclohex-2-en-1-ols (eq 24).[108]



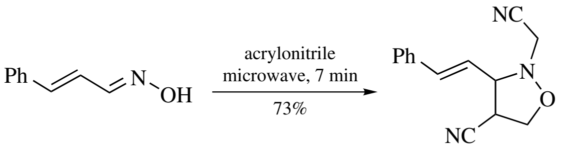
(24)

Silyl enol ethers and alkyl enol ethers will undergo [2 + 2] cycloadditions with acrylonitrile to form cyclobutanes. Alkynes have been shown to participate in similar processes to generate cyclobutenes. Aminoalkynes have been employed in this reaction, more recently the $AgNTf_2$-catalyzed [2 + 2] cycloadition of siloxy alkynes with acrylonitrile has been described (eq 25).[109]



(25)

Acrylonitrile will undergo a [2 + 2] cycloaddition with itself under thermal conditions. However, the process tends to be low yielding and proceeds with low stereoselectivity. When the reaction is carried out with irradiation and a nickel catalyst, *cis*-dicyanocyclobutane can be formed in reasonable yield.[110] Heterocyclic products are formed by the [3 + 2] cycloaddition of various 1,3-dipoles and acrylonitrile. Cyano pyrrolidines are the products when nitromethine ylides function as the 1,3-dipole.[111] Tetrahydroisoxazoles can be formed by the cycloaddition of acrylonitrile and nitrones. A recent example highlights the expeditious use of microwave reactors in the synthesis of a trisubstituted tetrahydroisoxazoline (eq 26).[112] A [5 + 2] cycloaddition between a functionalized 3-oxidipyrilium salt and acrylonitrile has been used as the key step in a recent synthesis of cyanotropanones.[113]



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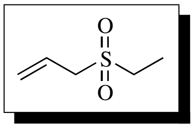
# Allyl Ethylsulfone



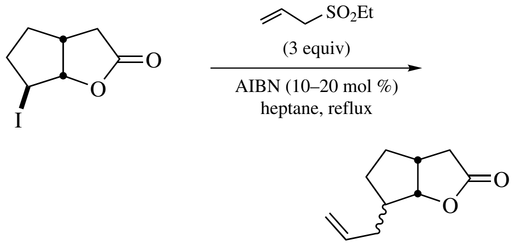
*[34008-91-8]* $C_5H_{10}O_2S$ (134.19)

(reagent used for the tin-free allylation of aliphatic iodides and xanthates under neutral conditions)

*Physical Data:* bp 124 °C. (14 mm Hg); $n_D^{22}$ 1.4721.
*Solubility:* sparingly soluble in water, but soluble in most organic solvents.
*Preparative Methods:* allyl ethylsulfone is easily prepared by oxidation of allyl ethylsulfide with 30% hydrogen peroxide/glacial acetic acid[1] or, better, with hydrogen peroxide and a catalytic amount of tungstic acid[2] or ammonium molybdate.[3] Allylation of zinc ethylsulfinate with allyl bromide has also been reported but is less efficient.[4]
*Purity:* the reagent is best purified by distillation under reduced pressure.
*Handling, Storage, and Precaution:* the reagent must be kept away from bases, which cause a shift of the olefinic bond to give the vinylic isomer; otherwise the reagent is handled like any other organic liquid. The toxicity is not known.

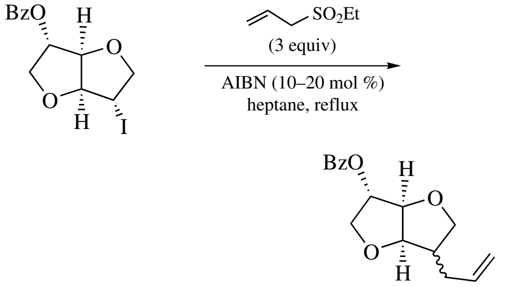
**Mechanism of the Allylation Reaction.** Allyl ethylsulfone is a reagent that allows the tin-free allylation of aliphatic iodides and xanthates. In order to better appreciate the scope and limitations of this allylation method, it is important to briefly examine its mechanism, shown in a simplified form below (eq 1).[5] An ethylsulfonyl radical, generated from the reagent through the agency of the initiator, extrudes sulfur dioxide to give a reactive ethyl radical. This species can exchange an iodine atom or a xanthate group from the substrate with the concomitant formation of radical $R^\bullet$, which then reacts with allyl ethylsulfone to give the desired allylated product and another ethylsulfonyl radical that propagates the chain. The extrusion of sulfur dioxide from ethylsulfonyl radicals is a comparatively slow and reversible process. It is favored by an increase in the reaction temperature and the gaseous sulfur dioxide normally escapes the refluxing reaction medium. The step involving exchange of iodine or xanthate is fast but also reversible and this introduces the main limitation to the method: radical $R^\bullet$ must be more stable than $Et^\bullet$ in order to drive the equilibrium forward. The procedure cannot therefore normally be used to allylate vinylic, or aromatic, iodides or xanthates since vinyl and aryl radicals are usually less stable than ethyl radicals. For primary substrates, where the stability of the corresponding radicals is similar to ethyl, the allylation may require an excess of allyl ethylsulfone. It may be advantageous in these instances to use allyl methylsulfone as the allylating reagent. Loss of sulfur dioxide in this case is slower, but a more energetic methyl radical is produced and the exchange equilibrium would tilt more in the desired direction. The choice of initiator depends on the reaction temperature and therefore on the boiling point of the solvent used. AIBN and lauroyl peroxide are suitable at around 70–90 °C, V-40 or VAZO [1,1′-azobis(cyclohexane-1-carbonitrile)] for the range 90–110 °C, cumyl peroxide for the range 100–130 °C, and di-*tert*-butyl peroxide for temperatures above 130 °C.

**Allylation of Iodides.** The allylation of iodides is illustrated in eqs 2–6.[5] Secondary and tertiary iodides are allylated readily, whereas primary iodides, as in the last example, react sluggishly and consume more reagent, for the reasons discussed in the preceding section (the yield based on recovered starting iodide is 70%). The solvent used is generally heptane or a mixture of heptane and chlorobenzene when the substrate is not very soluble in heptane alone. The ready availability of iodides through the iodolactonization reaction and other related transformations is a point worth noting.



(2)

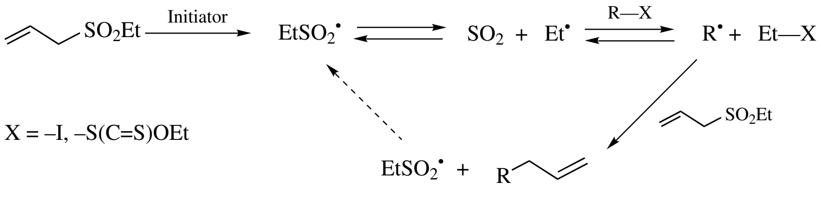
75%; *exo*:*endo* (85:15)



(3)

75%; *exo*:*endo* (10:1)

**Allylation of Xanthates.** The readily available xanthates, prepared for example by displacement of a leaving group with commercial potassium *O*-ethyl xanthate, are also effective substrates in the allylation process.[6] Unlike iodides, where the radical exchange is a one-step process, the transfer of a xanthate group



(1)