1 Introduction

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1.1 History of Alkynes

Alkyne is one of the fundamental functional groups that established the foundation of organic chemistry [1]. The smallest member of this family, acetylene, was first discovered in 1836 by Edmund Davy [2]. It was rediscovered and named "acetylene" by Marcellin Berthelot in 1860 by passing vapors of organic compounds through a red-hot tube or sparking electricity through a mixture of cyanogen and hydrogen gas. Acetylene is a moderately common chemical in the universe [3], often in the atmosphere of gas giants. In 1862, Friedrich Wöhler discovered the generation of acetylene from the hydrolysis of calcium carbide (Equation 1.1). Acetylene produced by this reaction was the main source of organic chemicals in the coal-based chemical industry era. When petroleum replaced coal as the chief source of carbon in the 1950s, partial combustion of methane (Equation 1.2) or formation as a side product of hydrocarbon cracking became the prevalent industrial manufacturing processes for acetylene. The next member of the family, propyne, is also mainly prepared by the thermal cracking of hydrocarbons. The first naturally occurring acetylic compound, dehydromatricaria ester (1), was isolated in 1826 [4] from an Artemisia species. Well over 1000 alkyne-containing natural products have been isolated since then, among which many are polyyne-containing natural products isolated from plants, fungi, bacteria, marine sponges, and corals [5].

1

$$CaC_2 + H_2O \longrightarrow H \longrightarrow H + Ca(OH)_2$$
 (1.1)

$$2CH_4 + (3/2)O_2 \longrightarrow H \longrightarrow H + 3H_2O$$
 (1.2)

H₃CO_____

Dehydromatricaria ester (1)

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 CH_3

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The higher members of alkynes are generally derived from the smaller homologs via alkyne homologation processes of the terminal alkynes (see Equation 1.8, below), while some alkynes are generated through elimination reactions with organic halides under basic conditions (Equation 1.3) [1]. A search in Sci Finder shows that >70 000 terminal alkynes and >10 000 internal alkynes are now commercially available from various sources.

1.2 Structure and Properties of Alkynes

Alkynes contain a tripe bond, composed of a σ -covalent bond formed from two sphybridized carbons and two π -bonds resulted from the overlapping of two orthogonal unhybridized p-orbitals on each carbon (2) [1]. Consequently, alkynes are generally rod-like. Cyclic alkynes are less common with benzyne as an important reactive intermediate in organic chemistry [6]. Acetylene is linear and intrinsically unstable under pressure due to its high compressibility as well as its propensity to undergo exothermic self addition reactions. Consequently, acetylene itself can explode violently at high pressure and the safe limit for acetylene is 103 kPa. Thus, acetylene is generally shipped in acetone or dimethyl formamide (DMF) solutions or contained in a gas cylinder with porous filling [7]. Acetylene has been used as a burning fuel and for illumination purposes in the late nineteenth century and early twentieth century [8]. In modern times, alkynes have found a wide range of applications ranging from organic electronic materials, metal-organic frame works (MOF), pharmaceutical agents, and others [9]. The linearity of the alkyne creates strain when an alkyne is part of a ring [10]. In spite of this fact, cyclopentyne, cyclohexyne, and cycloheptyne can be generated at least fleetingly, their existence being confirmed by in situ trapping, notably by 1,3-dipolar cycloadditions [11]. Cyclooctyne is still highly strained but has sufficient stability to be isolated and used in click chemistry to study biological processes [12].

1.3 Classical Reactions of Alkynes

The higher degree of unsaturation of alkynes compared to alkenes increases their reactivity toward addition to both alkenes and alkynes. In particular, virtually all additions of HX and RX to alkynes are exothermic. Consequently, these

stoichiometric addition reactions have been the basis of most reactions in the classical alkyne chemistry (Equation 1.4) [1]. These classical alkyne addition reactions include the additions of hydrogen, halogens, water, hydrogen halides, halohydrins, hydroborations, and others. With a stoichiometric amount of a strong oxidizing reagent such as $KMnO_4$, the addition may be followed by C-C cleavage to give the corresponding acids (Equation 1.5). Less reactive reagents can also be added through the use of a transition-metal catalyst. The unique electronic character of alkynes wherein their HOMO–LUMO gap is rather small makes them especially effective as coordinators to transition metals. Thus, they function as chemoselective functional groups for catalytic transformations. For example, catalytic addition of dihydrogen to alkynes can proceed to either alkenes or alkanes depending on the choice of the catalysts (Equation 1.6) [13]. Further, the hydroalumination [14], hydrosilylation [15], hydrostannylation [16], as well as carboalumination [17] represent important modern advances of the alkyne addition reactions.

$$R \xrightarrow{X-Y} \qquad X \xrightarrow{R} \qquad X \xrightarrow{R} \qquad X \xrightarrow{Y} \qquad (1.4)$$

X-Y: halogens, HX, HOH, HOCI, HBR₂, etc.

$$R \longrightarrow R \longrightarrow RCO_2H + HO_2CR'$$
(1.5)

$$R \xrightarrow{H_2} R \xrightarrow{H_2} \xrightarrow{H} \xrightarrow{H} \xrightarrow{H} \xrightarrow{H_2} R \xrightarrow{H_$$

A second class of reactions pertains to terminal alkynes. Due to the increased s-character, the alkynyl C–H bonds ($pK_a = 25$) are much more acidic than the corresponding alkenyl C–H bonds ($pK_a = 43$) and alkyl C–H bonds ($pK_a > 50$) [18]. Thus, base-promoted additions of terminal alkynes to carbonyl compounds can occur under different basic conditions, a process discovered over a century ago (Equation 1.7). Treatment of terminal alkynes with bases such as lithium amide, butyllithium, or Grignard or zinc reagents generates metal acetylides stoichiometrically, which can then react with different carbon-based electrophiles to produce various higher alkyne homologs in the classical synthetic chemistry (Equation 1.8) [1]. Such processes can be catalyzed to permit deprotonation with much weaker bases as in the coupling with aryl halides under Pd/Cu catalysis (Sonogashira reaction, see Equation 1.13).

$$R \longrightarrow H + \underset{R'}{\overset{O}{\longrightarrow}} \overset{Base}{\longrightarrow} \qquad R \longrightarrow \overset{OH}{\underset{R''}{\longrightarrow}} \qquad (1.7)$$

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1.4

Modern Reactions

Although the classical stoichiometric addition reactions, alkyne cleavage reactions, and homologation reactions have established the foundation of alkyne chemistry, a rebirth of interest derives from recent concerns regarding societal and ecological sustainability under the mantra of Green Chemistry [19], which emphasizes chemical transformations that are more atom economic [20] and chemoselective, thereby minimizing the use of protecting groups [21]. Furthermore, rapid developments in the field of chemical biology demand chemical transformations that are orthogonal to biological conditions and functionalities in bioorganisms and which can work efficiently under both in vitro and in vivo biological conditions [22]. Alkynes, being both good π -donors and π -acceptors for transition metals as well as being energy rich, can be effectively activated by a catalyst thereby lowering the energy barrier to proceed to the more stable products while being unreactive toward various biological elements. At the same time, they can be chemoselectively activated in the presence of most typical functional groups (e.g., hydroxyl and carbonyl groups as well as alkenes) and in protic solvents including water [23]. Such triggered reactivities are orthogonal to the classical reactivities and can be tuned to target specific desired reaction sites while maintaining tolerance toward other functionalities through the discrete choice of catalyst, which will greatly simplify the syntheses of complex compounds and allow direct modifications of biomolecules in their native states and ambient environment. Modern developments, in view of atom economy, can be represented by three major classes: (i) catalytic cyclization reactions, (ii) catalytic homologations of terminal alkynes, and (iii) catalytic isomerization reactions of alkyne.

Although alkyne oligomerization was known at a high temperature since the late nineteenth century [2], various cyclization reactions of alkynes catalyzed by transition metals are among the most important developments in modern alkyne chemistry. The most well-known examples include the transition-metal-catalyzed [2 + 2 + 2] cycloaddition reactions (Equation 1.9) [24], the Pauson–Khand-type reaction of alkyne–alkene–carbon monoxide (Equation 1.10) [25], the enyne cyclization reactions (Equation 1.11) [26], and the 1,3-dipolar cycloaddition such as that with azides (the archetypical Click reaction) (Equation 1.12) [27].



1.4 Modern Reactions 5



$$R \longrightarrow + N_3 - R' \xrightarrow{cat.} R \longrightarrow N - R'$$
(1.12)

The second major class of modern alkyne reactions is the catalytic transformation of terminal alkyne C-H bonds. Although homologation of terminal alkynes through the reactions of metal acetylides with organic halide is a classical alkyne reaction, such a reaction cannot be applied to aryl and vinyl halides due to their inert nature in nucleophilic substitution reactions. The development of catalytic coupling of terminal alkynes with aryl and vinyl halides (the Sonogashira reaction) has overcome this classical challenge and opened up a new reactivity mode in alkyne homologation (Equation 1.13) [28]. Complimentary to the classical Favorskii reaction (Equation 1.7), the modern development of catalytic direct addition of terminal alkynes to aldehydes provides great opportunities in generating optically active propargyl alcohols (Equation 1.14) [29]. The catalytic direct additions of terminal alkynes to imines (and derivatives) (Equation 1.15) [30] and conjugate addition to unsaturated carbonyl compounds (Equation 1.16) [31] represent other major achievements in modern alkyne reactions. On the other hand, the catalytic oxidative dimerization (Glaser-Hay coupling) [32] and simple alkyne dimerization (Equation 1.17) [33] which date from the late 1800s have become increasingly important in modern synthetic chemistry.

$$R \longrightarrow + X - Ar \xrightarrow{cat.} R \longrightarrow R \longrightarrow (1.13)$$











Two additional processes that have much unrealized potential in synthetic chemistry are the alkyne disproportionation (metathesis) and the alkyne redox isomerization reactions. Like the alkene metathesis, the catalytic alkyne–alkyne metathesis reaction retains all functionalities by switching the groups attached to the alkynes (Equation 1.18) [34]. Another unique atom-economic reaction of alkynes that is currently under-utilized but will have a great potential for future development is the "alkyne-zipper reaction" (Equation 1.19) [35]. Such reactions shift readily accessible internal alkyne triple bond to terminal positions for further homologations. A different type of "retaining functionality is found in the redox isomerization of propargyl alcohols to generate conjugated ketones" (Equation 1.20) [36].

$$R \longrightarrow R + R' \longrightarrow R' \xrightarrow{cat.} R \longrightarrow R' + R \longrightarrow R'$$

$$(1.18)$$



$$R' \xrightarrow{cat.} R' \xrightarrow{cat.} (1.20)$$

1.5 Conclusion

With the recent emphasis on sustainability and the ever increasing needs in synthetic efficiency, alkynes provide a truly unique functionality that is orthogonal to other functional groups, biological conditions, and ambient environment, yet can be selectively triggered to occur in a specific reaction mode with the absence of protecting groups or anhydrous conditions. Such reactions will have great potential to simplify synthetic chemistry and will find wide applications in chemical biology and organic materials. This book, comprising experts on related subjects, provides an overview of developments of modern alkyne reactions. Due to the limit of space, many other important developments in modern alkyne chemistry such as various catalytic conversions of alkyne triple bonds [37] and alkyne polymerizations [38] have not been covered in this book.

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