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Digest Paper

Terminal ynamides: synthesis, coupling reactions, and additions to common electrophiles

Andrea M. Cook, Christian Wolf*

Department of Chemistry, Georgetown University, Washington, DC 20057, USA

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ABSTRACT

Ynamides consist of a polarized triple bond that is directly attached to a nitrogen atom carrying a sulfonyl, an alkoxycarbonyl, an acyl, or another electron withdrawing group. The triple bond polarization renders ynamides broadly useful building blocks with synthetic opportunities that go far beyond traditional alkyne chemistry. The versatile reactivity of ynamides in cycloadditions, cycloisomerizations, regioselective additions with various nucleophiles or electrophiles, ring-closing metathesis, and many other reactions has been investigated in detail during the past decades. A common feature of these methods is that the triple bond is consumed and either cleaved or transformed to a new functionality. The wealth of reports on these ynamide reactions is in stark contrast to the dearth of carbon–carbon bond formations that leave the triple bond of terminal ynamides intact. The recent introduction of effective synthetic methods for the preparation of terminal ynamides has set the stage to fully explore the synthetic potential of this intriguing class of compounds. This digest Letter summarizes the most effective routes to terminal ynamides and the current state of selective nucleophilic addition, substitution, and coupling reactions, including the first examples of asymmetric synthesis.

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Introduction

The distinctive chemical properties and synthetic versatility of ynamines and ynamides have attracted rapidly increasing attention among synthetic chemists. The reactivity of the electron-rich, strongly polarized triple bond in ynamines and analogues thereof varies significantly from that of simple alkynes. Ynamines are rather unstable and readily hydrolyze toward amides, which complicates the synthesis, storage, and use of these intriguing building blocks. Because the presence of an electron withdrawing acyl or sulfonyl group effectively diminishes the triple bond polarization, ynamides have become practical alternatives that facilitate handling and improve reaction control (Fig. 1).

The emergence of ynamides in the last 20 years has created new synthetic opportunities and challenges at the same time. Internal ynamides exhibiting a *C*-substituted triple bond have been used in many reactions and have been applied in the total synthesis of natural compounds.[1] In stark contrast to alkynes, which have been

* Corresponding author.
E-mail address: cw27@georgetown.edu (C. Wolf).

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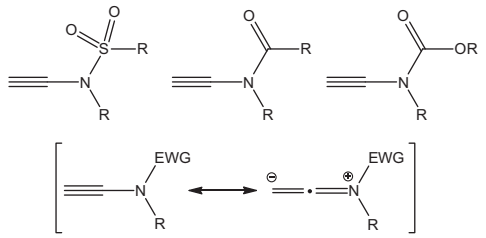
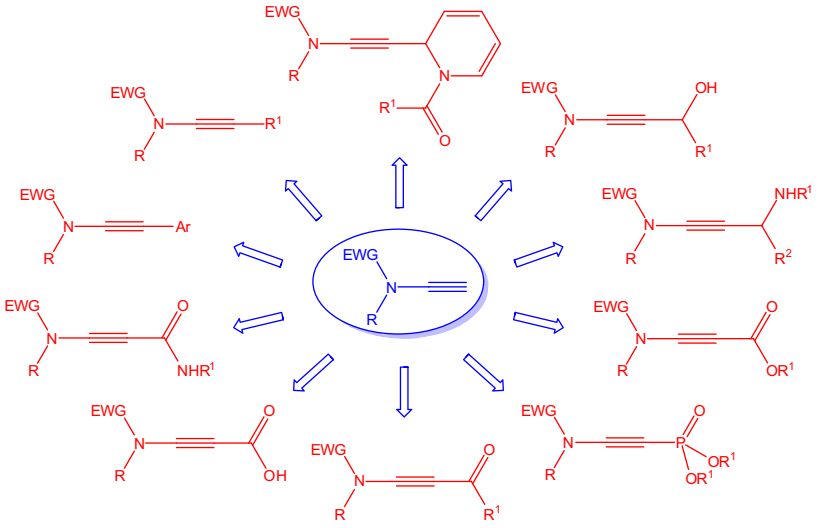


Figure 1. Structures of terminal ynamides.

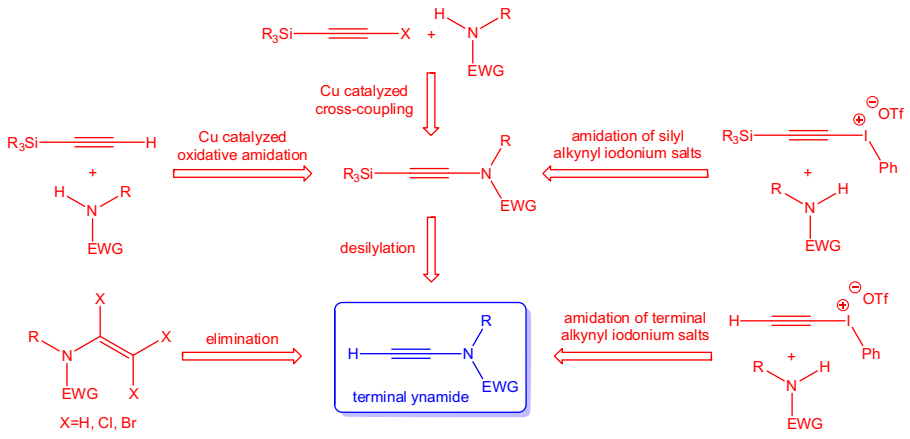
employed extensively in Sonogashira couplings and nucleophilic addition and substitution reactions, the utilization of substrates carrying a terminal ynamide functionality typically trails behind the development of synthetic methods that exploit the more popular internal analogues. As a result, the majority of reactions of terminal ynamides reported to date do not conserve the triple bond,[2] and cycloadditions,[3] cycloisomerizations,[4] Heck–Suzuki–Miyaura domino reactions,[5] ring-closing metathesis,[6] radical additions,[7] and titanium-mediated carbon–carbon bond formations are among the most common synthetic transformations.[8] Despite significant progress in the synthesis of terminal ynamides, carbon–carbon bond forming reactions that leave the triple bond intact are rare and have only recently been discovered (Scheme 1). This review discusses the current state of terminal ynamide synthesis and focusses on transformations that maintain the alkynyl motif.

Synthesis of terminal ynamides

To date, three major routes for the preparation of terminal ynamides have been developed.[1,9] The first viable syntheses of terminal ynamides were based on elimination reactions of dichloro or trichloro enamides with *n*-butyllithium at low temperatures and subsequent quenching of the reaction with alcohol. More recently, the use of alkynyl iodonium salts and the extension of copper catalyzed C–N bond formation to ynamide synthesis have significantly improved the general scope and functional group compatibility. The reaction between lithiated amides and electrophilic alkynyl iodonium salts is believed to proceed via alkylidene carbene intermediates which preferentially rearrange to the corresponding ynamides, vide infra. Trimethylsilylated alkynyl iodonium salts were initially used to form silyl ynamides which were then subjected to deprotection with TBAF, but it was later found that terminal ynamides can be made directly from terminal alkynyl iodonium salts. The key step in the third main pathway to terminal ynamides is the copper catalyzed amidative cross-coupling of alkynyl halides, alkynyl trifluoroborates, alkynyl bismuthonium salts, or terminal alkynes. In all cases, the alkyne moiety must be protected by a silyl group which is finally removed



Scheme 1. Overview of transformations of terminal ynamides leaving the triple bond intact.



Scheme 2. Synthetic routes to terminal ynamides.