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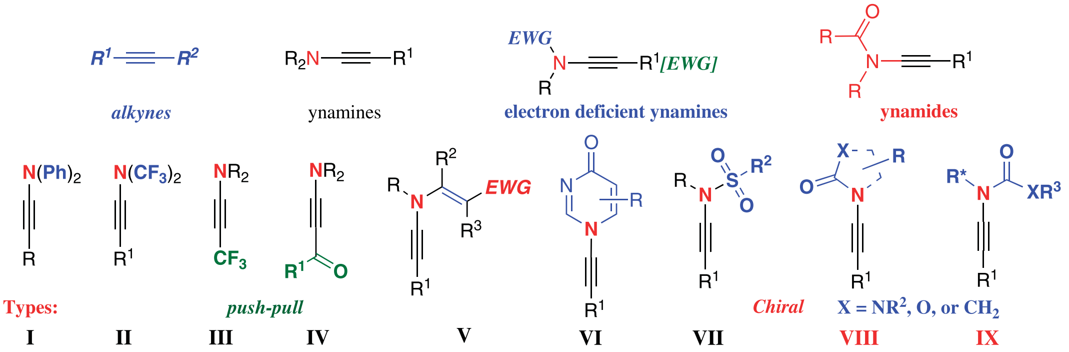
Preface

Chemistry of electron-deficient ynamines and ynamides

Ynamines [1-amino-alkynes or *N*-alkynyl amines] became synthetically one of the most useful subgroups of alkynes after the establishment of a practical synthesis in 1963. In the ensuing 20 years, reactivities of 1-amino-alkynes were thoroughly explored. However, unlike its close relative enamines, this synthetic prominence did not persist. The extent of synthetic applications of ynamines has suffered a dramatic decline during the last 20 years. The limited application of ynamines is largely due to the difficulties in their preparation and handling. Their unusual sensitivity toward hydrolysis and their high reactivity toward electrophiles have rendered traditional ynamines synthetically inaccessible in diversity. Diminishing ynamines' electron-density by substituting the nitrogen atom with an electron-withdrawing group, or through substitutions in the alkyne, represents a unique strategy for improving ynamines' stability, thereby regaining their usefulness in organic synthesis. These new generations of ynamines may be classified as electron-deficient ynamines [Type I–VI] and/or simply ynamides [Type VII–IX]. The concept of improving ynamine's thermal stability and stability toward hydrolytic conditions should be credited to Viehe who in 1972 reported the synthesis of the first ynamides [Type IX].



Despite the precedent of electron-deficient ynamines and ynamides, and their improved stability, it is not until recently have these functionally rich organic building blocks, especially ynamides, recaptured the attention of organic chemists. These recent developments and efforts have begun to revitalize interest within the synthetic community in utilizing nitrogen-substituted alkynes in organic synthesis, thereby providing an ideal timing for this special issue of Tetrahedron Symposium-in-Print focusing on the chemistry of electron-deficient ynamines and ynamides. Although regrettably this Symposium is missing some earlier chemistry from Professors Peter Stang [push–pull Type IV] and Ken Feldman [chiral ynamides Types VII and IX], pioneering work from Professors Bernhard Witulski and Jon Rainier on transition metal-mediated cycloadditions using ynamides of Type VII, and some enyne metathesis form Professor Javier Pérez-Castells, this issue is comprised of 14 outstanding contributions that provide an excellent coverage of different types of electron deficient ynamines and ynamides, and their syntheses as well as an array of impressive methodologies including the ultimate goal of applying their chemistry to the natural products synthesis.

This symposium contains: (1) Ishihara's excellent fluorine chemistry on both the synthesis and reactivities of *N*,*N*-dialkyl(3,3,3-trifluoro-1-propynyl)amines [push–pull Type III]: the reactivities included additions of halogens and formally a hetero metathesis process with aldehydes. (2) Katritzky's concise synthesis of 1-(2,2-dichlorovinyl)benzotriazole [Type VI] and its subsequent lithiation–substitution with a range of electrophiles, thereby precisely demonstrating the principle of attaining highly functionalized electron-deficient ynamines or ynamides from the terminally unsubstituted system [or the parent system]. (3) Kerwin's nifty thermolysis of 1,2-dialkynylimidazoles [Type VI] in an aza-Bergman-like cyclization that led to some very interesting mechanistic observations as well as useful heterocycles such as imidazolyl–pyridines. (4) Brückner's clever solution to the synthesis of *N*-ethynyl-tosyl-amides [a parent system for Type VII], which had been a challenge.

A range of cycloadditions, cyclizations, and annulations are described here. These contributions include: (1) Danhesier's elegant [2+2] ketene-cycloadditions that gave an array of substituted 3-amino-cyclobut-2-en-1-ones: this work also reiterates details and the elegance of the copper-promoted

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N-alkynylation of carbamates and sulfonamides in the preparations of ynamides [Type VII–IX]. (2) Tam's clever ruthenium-catalyzed diastereoselective [2+2] cycloadditions between bicyclic alkenes and chiral ynamide: this work further demonstrates that the ynamide moiety with an improved stability could readily survive conditions involving transition metals. (3) Cintrat's fine work on the first examples of highly regioselective 'click reaction' employing *N*-benzyl-*N*-tosyl-ynamide and various highly functionalized azides in a [3+2] cycloaddition manner. (4) Saá's copper-catalyzed dimerization of *N*-aryl- or *N*-alkyl-tosyl-ynamides in the preparations of *N*,*N*′-aryl- and *N*,*N*′-alkyl-buta-1,3-diyne-1,4-di-tosyl-amides. In this paper, Negishi couplings of *N*-ethynyl(zinc)-tosyl-amides with heteroaryl iodides were shown to afford *N*-aryl- and *N*-alkyl-*N*-aryl-ynamides. In addition, an intramolecular dehydro-[4+2] cycloaddition reaction of ynamides was shown to be feasible to provide novel benzannulated and heteroannulated carbazoles. Three separate topics on reactions of ynamides for the price of one. (5) Malacria's beautiful radical cascade that entailed a *5-exo-dig* cyclization followed by a *6-endo-trig* radical trapping to transform ynamides into an array of nitrogen heterocycles. In addition, a formally [2+2] cycloaddition of ene-tosylynamides could be promoted with Pt(II). Two very interesting synthetic methods employing ynamides are presented in one paper. (6) Mori's pioneering ring-closing metathesis of ene-ynamide employing a second-generation Ru–carbene complex that led to nitrogen-containing heterocycles with a dienamide motif that can undergo various Diels–Alder cycloadditions to give highly functionalized indoles or quinolines. (7) Cossy's elegant synthesis of 3-(arylmethylene)-isoindolin-1-ones from various ynamides and boronic acids via a Heck–Suzuki–Miyaura domino sequence: this methodology was applied to the total synthesis of lennoxamine, which constitutes as the first example of ynamides as a key intermediate in the natural product synthesis. It is highly noteworthy that many of these studies demonstrate a key principle or significance advantage of 1-amino-alkynes over simple alkynes: the nitrogen atom remains a key component of various reaction products.

Last but not the least, this Symposium also includes: (1) Urabe's elegant usage of acetylene–titanium complexes generated from *N*-(1-alkynyl)sulfonamides and $Ti(O\text{-}i\text{-}Pr)_4$/*i*-PrMgCl in highly regio- and diastereoselective additions to aldehydes that afforded allylic alcohols. In addition, inter- or intramolecular coupling reaction with acetylenes or olefins using also $Ti(O\text{-}i\text{-}Pr)_4$/*i*-PrMgCl led to stereoselective syntheses of various (sulfonylamino)dienes. This work further supports copper(I)-catalyzed amidations of 1-bromo-1-alkynes as an efficient protocol in the synthesis of *N*-(1-alkynyl)sulfonamides. This represents another paper that contains two elegant bodies of work. (2) Zhang's highly regio- and stereoselective Brønsted acid-catalyzed coupling of ynamides with pyrroles, furans, and indoles, which represents an equivalent of hydro-arylation of ynamides. Finally, (3) Hsung's work on a Brønsted acid-catalyzed highly diastereoselective Saucy–Marbet rearrangement using chiral ynamides and propargyl alcohols, leading to interesting mechanistic understanding this pericyclic rearrangement as well as a highly diastereoselective synthesis of chiral allenes.

These 14 contributions literally have provided 20 or more syntheses, methods, and applications! I thank all the contributing authors for making this Symposium possible and bailing me out, and Professor Harry Wasserman for providing this invaluable opportunity to organize this Symposium and for his guidance and patience throughout this entire process for which I was completely clueless.

We hope that this Symposium can firmly illustrate that the chemistry of ynamines is actually alive and well but in the forms of electron-deficient ynamines and ynamides. They have achieved the right balance between reactivity and stability, allowing them to be handled easily, thereby leading to highly stereoselective and intramolecular reactions that otherwise would be very difficult to accomplish using traditional ynamines. With such a compelling evidence for the reemergence of the ynamine chemistry, we hope that an even greater interest will come forth in the near future, leading to new methodologies employing electron-deficient ynamines and ynamides.

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