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Extended Abstract

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Alkyne annulation: Step-economic construction of core structures of natural products and drugs

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We are interested in development of the applications of alkynes in the synthesis of carboand heterocyclic compounds via their annulation with high-atom utilization and step-economy. In this presentation, we would like to report the recently developed protocols for the synthesis of natural products such as Precocene I (from Ageratum houstonianum), Cassiarin C (from Cassia siamea) from the cyclocondensation of alkynes with the activation of C-H bonds, and the synthesis of the drugs such as h5-HT2A antagonist and RITA. These synthetic protocols have the significant advantages of easily available starting materials, efficient and stepeconomic processes. Polycyclic scaffolds are omnipresent in natural products and drugs, and the synthetic strategies and methods toward construction of these scaffolds are of particular importance. Compared to simple cyclic ring systems, polycyclic scaffolds have higher structure complexity and diversity, making them suitable for charting broader chemical space, yet bringing challenges for the syntheses. In this review, we surveyed progress in the past decade on synthetic methods for polycyclic natural product scaffolds, in which the key steps are one-pot reactions involving intermolecular or intramolecular alkyne annulation. Synthetic strategies of selected polycyclic carbocycles and heterocycles with at least three fused, bridged, or spiro rings are discussed with emphasis on the synthetic efficiency and product diversity. Recent examples containing newly developed synthetic concepts or toolkits such as collective and divergent total synthesis, gold catalysis, C–H functionalization, and dearomative cyclization are highlighted. Finally, several "privileged synthetic strategies" for "privileged polycyclic scaffolds" are summarized, with discussion of remained challenges and future perspectives. Natural products and their synthetic analogs have a broad range of biological activities, and they are essential sources of drug and drug candidates. They are also a powerful toolkit for studying complex biological systems, including probing protein functions. Among them, polycyclic natural products (PNPs) are particularly attractive for their complex scaffolds with well-arranged functional group, as well as unique responses and diverse interactions with biological systems, which can be treated as a large class of privileged structures for drug discovery. Complex PNPs such as strychnine continuously spur the development of new synthetic strategies, reactions, and reagents for ring construction. Successful examples of PNPs in pharmaceutical industry, such as morphine, cortisone, camptothecin, vincristine, and paclitaxel (Taxol), have encouraged the syntheses of natural products derivatives and analogs for investigating quantitative structure–activity relationship. With increasing demands for high-throughput screening and navigating medicinal relevantly chemical space, development of efficient annulative reactions is a core task aiming for rapid access to molecular complexity, scaffold diversity, and desired function that is comparable or even superior to PNPs. By integrating multistep synthetic sequences in one pot, tedious workup and purification procedures can be avoided, thus reducing the amounts of solvent and waste, as well as saving time, labor, and cost. As a result, both efficiency and sustainability are improved along with the increase of pot economy reported an elegant synthesis of progesterone, in which a biomimetic cation-π cyclizations of an alkyne–polyolefin substrate was achieved for one-pot construction of the entire polycyclic steroid scaffold. This landmark work stimulated the successors to develop a range of cascade/domino/tandem reactions for construction of PNPs. Besides using multifunctional substrates, one-pot cyclizations can be also realized by multicomponent reactions, which are also powerful for synthesis of PNPs and construction of natural product–like molecules in a modular and combinatorial fashion. Alkyne-based building blocks are widely used for cyclization because of their rich reaction activities and tunable cyclization modes under different conditions. The fruitful alkyne chemistry has been exploited for construction of molecules with various molecular shapes and functional groups, resulting in mighty ability for generating molecular complexity and diversity with high atom economy. Especially, when one of the two π bonds are *syn*-difunctionalized, alkynes can be transformed to endocyclic double bonds and serve as C2 synthons for substituted (aromatic) carbocycles and heterocycles. When both of the π bonds are reacted, alkynes can be employed for construction of sp^3 centers, which exist in numerous PNPs with three-dimensional scaffolds. Although significant progress has been made for assembly of monocyclic and bicyclic molecules via alkyne annulation, it is still challenging for efficient construction of polyheterocycles. Multiple reactive sites or components may interact on each other, making it difficult to balance the reactivity and selectivity for several successive steps in one pot. In the past two decades, we have witnessed blossoming of new synthetic toolkits including C–H functionalization. These emerging synthetic methodologies enable new cascade reaction in mild conditions via substrate activation (for alkynes, their reaction partners, or both of them), thus expanding the utilization of alkynes for syntheses of polyheterocycles with higher efficiency and diversity. In this review, recent progress in the past decade (2010–2020) in either total synthesis of natural products and synthetic methodologies for construction of natural product–like molecules are surveyed and illustrated by selected examples. Although scaffolds by connection of several simple rings are also prevalent and important, the polycyclic scaffolds discussed here are mainly those with at least three fused, bridged, or spiro rings. For the syntheses, we would like to focus on cascade cyclizations involving three or more reactive sites or components including at least one alkyne, while transformations in one-pot two-stage fashion are also included. As the efficiency for generation of complexity and diversity is the most concerned issue in this review, the one-pot ring-forming step for assembly of the polycyclic ring systems is highlighted, while detailed total synthesis and common substrate scope will not be shown.

Synthesis of PNPs using arynes, which has been well-discussed in a recent review, is not covered herein, except for works using alkynes for *in situ* generation of the aryne intermediates. Recently, Echavarren's group reported a gold(I)-catalyzed double cyclopropanation using acetylene as a unique dicarbene equivalent. A 3/6/3 fused tricyclic scaffold can be formed in a diastereoselective way by employing 1,5-dienes as substrates, which can be used for one step total synthesis of waitziacuminone from geranyl acetone. In this work, three rings with four new four C–C bonds are constructed in one pot. Notably, the acetylene gas is also produced in one pot, in which the "pot" is an upside-down Y-shaped two-chamber flask. Acetylene is generated *in situ* from calcium carbide and water in one chamber of the flask and then diffuses to the other chamber and dissolved in DCM to participate in the organic reaction. This kind of two-chamber one-flask reaction maintains practical advantages of traditional one-pot reactions and overcomes some disadvantages of reaction control, which would largely increase the modality and extend the boundary of one-pot reactions. Yu's group reported a cascade cyclization for polycyclic carbocycles via gold(I)-catalyzed sequential cyclopropanation, cope rearrangement, and C–H functionalization of linear dienediyne substrates. A 6/7/5-fused tricyclic skeleton can be obtained, which exists in some natural diterpenes such as daphnane and tigliane families. The reaction proceeds well using substrates with nitrogen- or oxygen-containing linkers, but was not suitable for a malonate-tethered substrate. Recently, they performed density functional theory calculations and experimental studies to investigate the reaction mechanism, which unveiled the origin of different reactivity of substrates with various tethers. Based on the obtained mechanistic insights, prediction was made and then was tested by experiments, leading to a new methods to access 5/7/5-fused and 5/7/6/6-fused carbocycles via cascade cyclizations involving aliphatic or aromatic C–H insertion, respectively. This work also demonstrates the promising power of computational chemistry for the development of new reactions. Domino ring-closing metathesis (RCM) can be employed for syntheses of a range of polycyclic carbocycles from well-arranged dienyne substrates. Taxol, one of the most famous anticancer drugs, is among the blockbuster drugs together with its derivatives and to be an attractive synthetic target. Prunet's group investigated the synthesis of taxane and isotaxane derivatives, during which the tricyclic carbocycles were constructed via domino RCM of ene–yne–ene substrates. In the next year, reported one-step assembly of a taxane-like skeleton from an ene–yne–yne–ene substrate. In some cases, the domino RCM sequence may be blocked, and intermediate products were obtained because of high steric hindrance, ring strains, and active functional groups, as well as loss of activity of the catalyst for multiple steps. Therefore, adjustment of the substrates and optimization of the catalytic systems are needed.

Bottom Note: *This work is partly presented at* 6th World Congress on NATURAL PRODUCT & SYNTHETIC CHEMISTRY June 24-25, 2019 | New York, USA.