ORGANIC LETTERS

2013
Vol. 15, No. 15
4026–4029

Synthesis of High-Value 1,6-Enynes by Tandem Fragmentation/Olefination

Tung T. Hoang and Gregory B. Dudley*

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390, United States

gdudley@chem.fsu.edu

Received July 1, 2013

ABSTRACT

A tandem process provides high-value 1,6-enynes that are otherwise difficult to prepare. Two base-mediated reactions—fragmentation and olefination—are executed in a coordinated manner that is overall more efficient than either reaction on its own. The 1,6-enynes can be strategically employed in conjunction with carbocyclization to deliver important targets, as noted for reported syntheses of hirsutene and illudol.

Carbocycle construction is one of the enduring goals of organic synthesis. Many annulation and cycloisomerization strategies[1] leverage the thermodynamic potential energy of alkenes and alkynes to drive the formation of new rings and associated C−C bonds (Figure 1). Unsaturated hydrocarbon building blocks are the foundation of these strategies; the current work is focused on the efficient preparation of such high-value hydrocarbon systems.

We have been developing ring-opening fragmentation reactions that produce diverse keto-alkyne building blocks (Scheme 1).[2,3] These triflate-centered[4] studies build on the pioneering work of Eschenmoser, Coke, and others[5] and perhaps foreshadow recent efforts to produce allenes.[6] Our ongoing methodology[7] is proving useful for synthesis.[8] Here we describe the new strategic pairing of a related fragmentation reaction[9] with olefination, to deliver 1,6-enyne hydrocarbons that are otherwise difficult to prepare. Potential impacts on, for example, the synthesis of sesquiterpene natural products are noted.

The central objective of this methodology is to provide general and efficient access to high-value[10] 1,6-enynes. Most 1,6-enynes employed in carbocyclization methodologies

(1) Select reviews: (a) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 2899. (b) Toullec, P. Y.; Michelet, V. *Top. Curr. Chem.* **2011**, *302*, 31. (c) Zhang, L.; Sun, J.; Kozmin, S. *Adv. Synth. Catal.* **2006**, *348*, 2271. (d) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326.

(2) (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028. (b) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499. (c) Tummatorn, J.; Dudley, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 5050. (d) Tummatorn, J.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 1572. (e) Batsomboon, P.; Gold, B. A.; Alabugin, I. V.; Dudley, G. B. *Synthesis* **2012**, *44*, 1818.

(3) Other recent work on alkynogenic fragmentations: (a) Draghici, C.; Brewer, M. *J. Am. Chem. Soc.* **2008**, *130*, 3766. (b) Jabre, N. D.; Brewer, M. *J. Org. Chem.* **2012**, *77*, 9910. (c) Fleming, I.; Ramarao, C. *Org. Biomol. Chem.* **2004**, *2*, 1504–1510. (d) Boutillier, P.; Zard, S. Z. *Chem. Commun.* **2001**, 1304–1305.

(4) Vinylogous acyl triflate review: Chassaing, S.; Specklin, S.; Weibel, J.-M.; Pale, P. *Tetrahedron* **2012**, *68*, 7245.

(5) (a) Eschenmoser, A.; Frey, A. *Helv. Chim. Acta* **1952**, *35*, 1660. (b) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708. (c) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943. (d) Coke, J. L.; Williams, H. J.; Natarajan, S. *J. Org. Chem.* **1977**, *42*, 2380. (e) Shimizu, M.; Ando, R.; Kuwajima, I. *J. Org. Chem.* **1981**, *46*, 5246. (f) Fleming, I.; Ramarao, C. *Org. Biomol. Chem.* **2004**, *2*, 1504.

(6) (a) Kolakowski, R. V.; Manpadi, M.; Zhang, Y .; Emge, T . J.; Williams, L. J. *J. Am. Chem. Soc.* **2009**, *131*, 12910. (b) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 8962.

(7) (a) Kamijo, S.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 175. (b) Jones, D. M.; Lisboa, M. P.; Kamijo, S.; Dudley, G. B. *J. Org. Chem.* **2010**, *75*, 3260. (c) Tummatorn, J.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 158.

(8) (a) Jones, D. M.; Kamijo, S.; Dudley, G. B. *Synlett* **2006**, 936. (b) Jones, D. M.; Dudley, G. B. *Synlett* **2010**, 223. (c) Jones, D. M.; Dudley, G. B. *Tetrahedron* **2010**, *66*, 4860. (d) Tummatorn, J.; Batsomboon, P.; Clark, R. J.; Alabugin, I. V.; Dudley, G. B. *J. Org. Chem.* **2012**, *77*, 2093. (e) Tummatorn, J.; Diaz Muñoz, G.; Dudley, G. B. *Tetrahedron Lett.* **2013**, *54*, 1312. (f) Lisboa, M. P.; Jones, D. M.; Dudley, G. B. *Org. Lett.* **2013**, *15*, 886.

(9) Kamijo, S.; Dudley, G. B. *Tetrahedron Lett.* **2006**, *47*, 5629.

(10) We use the term "high-value" to reflect our perception that improved access to these specific alkyne building blocks will enhance the impact of strategies based on alkyne chemistry. In particular, neopentyl-tethered 1,6-enynes are needed for *gem*-dimethylcyclopentane natural products (cf. Figure 1; efficient synthetic routes to these targets are exemplified herein).

10.1021/ol401839e
Published on Web 07/25/2013

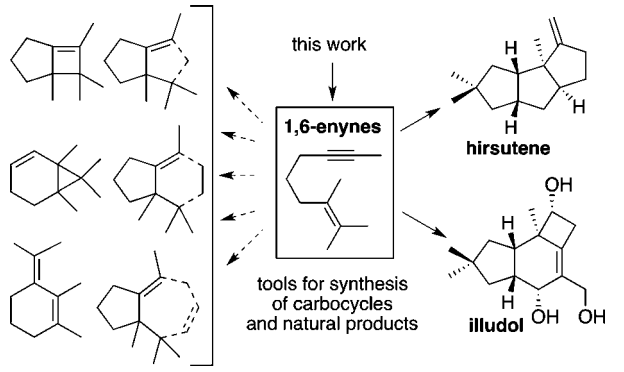
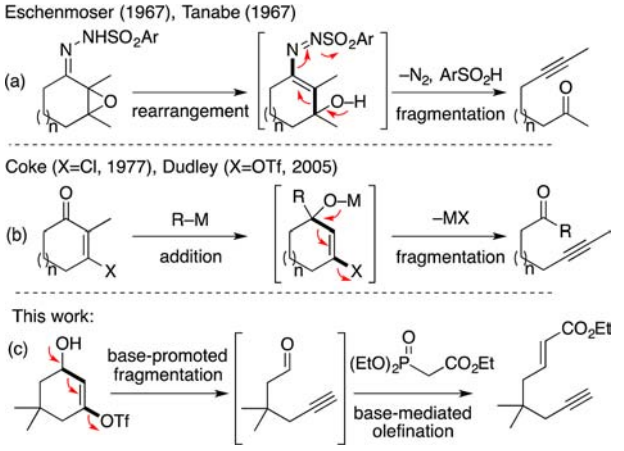


Figure 1. Versatility of 1,6-enynes for synthesis carbocycles and of natural product target structures.

Scheme 1. Selected Ring-Opening Fragmentation Reactions

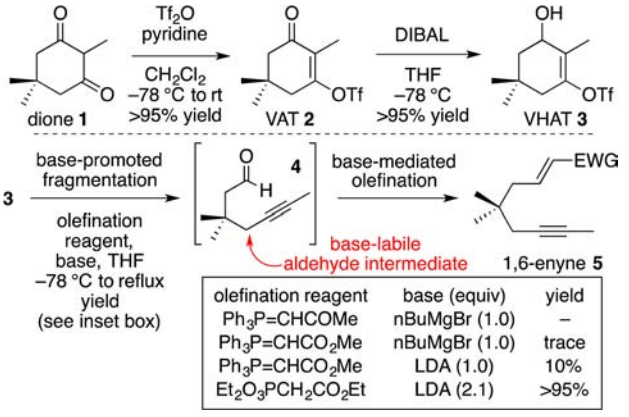


feature malonate- and heteroatom-tethered π-systems, typically because they are easier to prepare (e.g., by nucleophilic substitution reactions) than their hydrocarbon-tethered counterparts. However, the elusive hydrocarbon-tethered enynes are arguably more valuable for preparing the carbocyclic framework of most natural product targets.

We designed an original fragmentation/olefination process (Scheme 1c) to access hydrocarbon-tethered 1,6-enynes more efficiently. This process requires tandem orchestration of orthogonal reaction pathways: the olefination reagent must not interfere with fragmentation but must intervene immediately upon formation of the base-labile aldehyde.

The results of our initial screening and optimization are outlined briefly in Scheme 2. We focused on 3,3-dimethyl-

Scheme 2. Synthesis of Vinylogous Hemiacetal Triflate (VHAT) **3** and Initial Fragmentation/Olefination Studies[a]



olefination reagent	base (equiv)	yield
$Ph_3P{=}CHCOMe$	nBuMgBr (1.0)	–
$Ph_3P{=}CHCO_2Me$	nBuMgBr (1.0)	trace
$Ph_3P{=}CHCO_2Me$	LDA (1.0)	10%
$Et_2O_3PCH_2CO_2Et$	LDA (2.1)	>95%

[a] See Supporting Information for details.

5-heptynal (**4**), a valuable and prohibitively expensive synthetic building block.[11] 2-Methyldimedone (**1**)[12] can be converted into vinylogous acyl triflate (VAT) **2** in essentially quantitative yield[13] using our established protocol.[14] Reduction of **2** with DIBAL provides vinylogous hemiacetal triflate (VHAT) **3**, also in high yield. We explored several combinations of bases and olefination reagents, with the aim of generating and then trapping aldehyde **4** in a tandem fragmentation/olefination process. After unsatisfactory results with stabilized Wittig reagents, success was achieved using the combination of excess lithium diisopropylamide (LDA) and a Horner–Wadsworth–Emmons (HWE) reagent. Thus, VHAT **3** and triethyl phosphonoacetate were added in succession to a cold solution of LDA, followed by warming to produce 1,6-enyne **5**. Presumably, the anion derived from **3** fragments slowly to alkynyl aldehyde **4**, which then reacts quickly with the lithiated phosphonate to give **5**.

What is remarkable about this tandem process is that the overall yield (> 95%) exceeds what one would expect for either step independently. We have found that aldehydes (e.g., **4**) cannot be isolated in reasonable yield using our fragmentation methodology. Likewise, HWE olefination of enolizable aldehydes under strongly basic conditions is not typically this efficient.[15,16] The tandem process features slow generation of the aldehyde, with immediate trapping by the HWE reagent. The low steady-state concentration suppresses aldehyde oligomerization in favor of the (desired) olefination.

(11) Heptynal **4** was previously prepared in six steps (26% overall): Johnson, W. S.; Buchanan, R. A.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 504.

(12) Clark, R. D.; Ellis, J. E.; Heathcock, C. H. *Synth. Commun.* **1973**, *3*, 347.

(13) All yields refer to isolated and purified material judged to be ≥95% pure by ^{1}H NMR; see Supporting Information. For a discussion of the limits of precision in calculating yields, see: Wernerova, M.; Hudlicky, T. *Synlett* **2010**, 2701.

(14) Lisboa, M. P.; Hoang, T. T.; Dudley, G. B. *Org. Synth.* **2011**, *88*, 353.

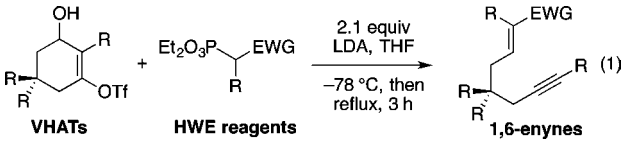
(15) Gu, Y.; Tian, S. K. *Top. Curr. Chem.* **2012**, *327*, 197.

(16) An analogous HWE olefination of 3,3-dimethyl-5-hexenal, for example, was recently reported in 83% yield; see: Jiao, L.; Yuan, C.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 4421.

(17) (a) Ho, T. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Li, J.; Lee, D. *Eur. J. Org. Chem.* **2011**, 4269. (c) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

The efficient synthesis of 1,6-enyne **5** underscores one of the advantages of tandem processes:[17] expanded utility of reactive and/or unstable intermediates. In this case, the intermediate aldehyde is unstable to basic reaction conditions and cannot be isolated in good yield, but the tandem process allows two base-mediated events to occur in high chemical yield. Tandem and related processes also aid in the design and execution of shorter syntheses, with corresponding reductions in waste and consumption of raw materials.[17]

The optimal coupling procedure described above (**3**→**5**, Scheme 2) was then generalized to prepare a representative collection of 1,6-enynes (eq 1 and Figure 2). VHATs **3a** and **3b** are each available in nearly quantitative yield over two steps from commercially available cyclic diones.[13] HWE reagents featuring esters, nitriles, ketones, amides, and tethered alkynes[7b] were all effective, providing the corresponding 1,6-enynes in good to excellent yields (Figure 2). The alkene geometry is set during the olefination stage of the tandem process. Consistent with general HWE reaction trends, thermodynamically preferred *E*-alkenes were obtained selectively in all cases. Ester-derived 1,6-enynes were generally prepared in the highest yields (**5a**–**d**, up to >95% yield), whereas ketone-derived 1,6-enynes consistently emerged in slightly reduced yields (**5g**–**l**, 65–75%, Figure 2). *E*/*Z* Selectivities in ester and ketone categories were at least 9:1, with the exception of **5d**. Nitrile-derived 1,6-enynes **5e** (85%) and **5f** (83%) were obtained in good yields but with reduced stereocontrol, which likely reflects the minimal steric profile of the nitrile group. Weinreb amides **5m** (74%) and **5n** (72%), in contrast, were isolated as single stereoisomers to the limits of NMR detection; Weinreb amides[18] create opportunities for further elaboration to diverse ketones and aldehydes (vide infra).



These 1,6-enynes, and especially the neopentyl-tethered 1,6-enynes (**5b**, **5d**, **5f**, **5h**, etc.), fill a critical gap between the methodological development of enyne cyclization reactions[1,19] and prospective applications to the synthesis of carbocyclic goal structures. Most developmental work features malonate- and heteroatom-tethered 1,6-enynes, but such functionalities do not necessarily align with carbocyclic targets. On the other hand, neopentyl-tethered 1,6-enynes give rise to *gem*-dimethylcyclopentanes, which are ubiquitous in terpenoid natural products.[20]

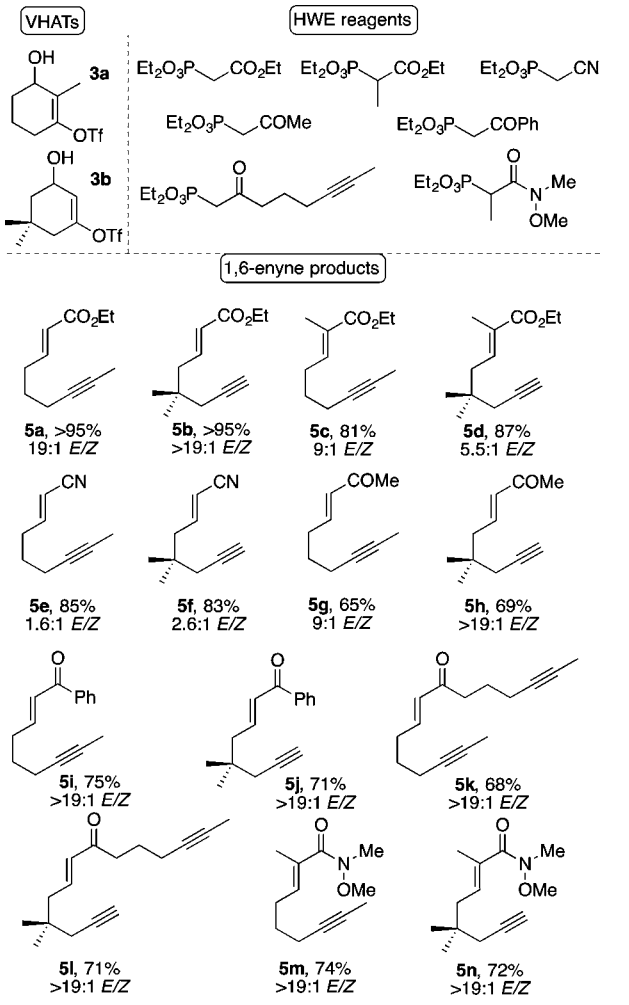


Figure 2. VHAT and HWE starting materials (top) and 1,6-enyne products (bottom) associated with eq 1, with product yields and stereoselectivities. See Supporting Information for details.

Various synthetic applications of these high-value 1,6-enynes can be envisioned; two are highlighted here. First, ethyl ester **5d** can be reduced to **6** (Scheme 3, top), a key intermediate in Oppolzer's synthesis of the classic sesquiterpene target, hirsutene.[21] Second, reduction of Weinreb amide **5n** and propargylation[22] yield endiyne **7** (Scheme 3, bottom), a pivotal intermediate that marks the halfway point in Vollhardt's 18-step synthesis of (±)-illudol.[23c]

These examples reflect the well-established importance of 1,6-enynes as cycloisomerization and annulation substrates in target-oriented synthesis, and they illustrate

(18) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(19) Three recent examples: (a) Hong, X.; Liu, P.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 1456. (b) Ishida, M.; Tanaka, K. *Org. Lett.* **2013**, *15*, 2120. (c) Brooner, R. E. M.; Brown, T. J.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6259.

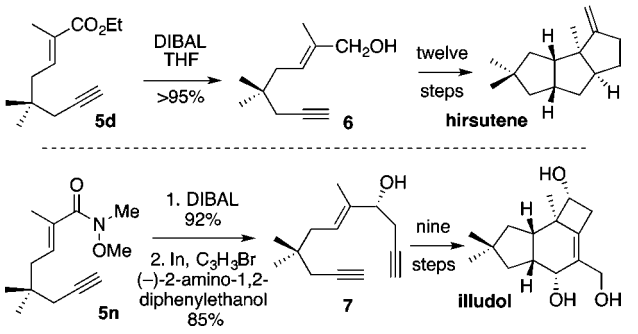
(20) Wang, G.; Tang, W.; Bidigare, R. R. Terpenoids as therapeutic drugs and pharmaceutical agents. In *Natural Products: Drug Discovery and Therapeutic Medicine*; Zhang, L., Demain, A. L., Eds.; Humana Press: Totowa, NJ, 2005; Chapter 9, pp 197–227. (b) Annual review: Fraga, B. M. *Nat. Prod. Rep.* **2012**, *29*, 1334 and references cited.

(21) Oppolzer, W.; Robyr, C. *Tetrahedron* **1994**, *50*, 415.

(22) Hirayama, L. C.; Dunham, K. K.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 5173.

(23) Syntheses: (a) Matsumoto, T.; Miyano, K.; Kagawa, S.; Yu, S.; Ogawa, J.; Ichihara, A. *Tetrahedron Lett.* **1971**, *12*, 3521. (b) Semmelhack, M. F.; Tomoda, S.; Hurst, K. M. *J. Am. Chem. Soc.* **1980**, *102*, 7567. (c) Johnson, E. P.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381. (d) Siengalewicz, P.; Mulzer, J.; Rinner, U. *Eur. J. Org. Chem.* **2011**, 7041.

Scheme 3. Facile Entries into the Oppolzer Synthesis of Hirsutene (Top) and Vollhardt Synthesis of Illudol (Bottom)[a]



[a] See Supporting Information for details.

how access to 1,6-enyne hydrocarbons has an instant impact on the strategic application of such methodologies. 1,6-Enynes **6** and **7** were originally prepared in seven and nine steps, respectively; now they are available in four and five high-yielding steps from dimedone. Our route to **7** formally establishes the shortest[24] synthesis of illudol.[23]

In summary, a new tandem process for the synthesis of high-value 1,6-enynes is reported. The coordinated execution of base-promoted fragmentation of vinylogous hemiacetal triflates and base-mediated olefination of the resulting alkynyl aldehydes provide convenient and efficient access to 1,6-enynes that are otherwise difficult to prepare. The resulting enynes will enable cycloisomerization and annulation strategies for preparing prominent targets, as exemplified here for hirsutene and illudol. Further exploration of tandem fragmentation/olefination processes, including the use of complementary tactics and application to other problems in chemical synthesis, is in progress.

Acknowledgment. The authors thank the Florida State University, the National Science Foundation (NSF-CHE 1300722), and the Vietnam Education Foundation (VEF Fellowship for T.T.H.) for generous financial support.

Supporting Information Available. Experiment procedures and characterization data of all new compounds. The material is available free of charge via the Internet at http://pubs.acs.org.

(24) Alcohol **7** was obtained in 87:13 er (unoptimized). Efforts to improve this ratio en route to what would be the first enantioselective synthesis of illudol are planned.

The authors declare no competing financial interest.