Intramolecular [4 + 2] Cycloaddition Reactions of Conjugated Ynones. Formation of Polycyclic Furans via the Generation and Rearrangement of Strained Heterocyclic Allenes

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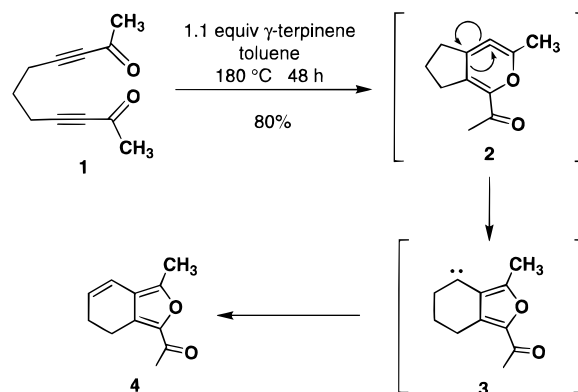*Cambridge, Massachusetts 02139*

Variants of the Diels−Alder reaction leading to heterocyclic systems represent an important extension of this most powerful of all ring-forming reactions.[1] Recently, [4 + 2] cycloadditions of conjugated enynes have emerged as a valuable strategy for the construction of aromatic and dihydroaromatic six-membered carbocycles.[2,3] Herein we describe the first heterocyclic variant of this process, the intramolecular [4 + 2] cycloaddition of conjugated ynones. The initial products of this reaction are highly strained heterocyclic allenes which undergo an unusual rearrangement leading to the formation of polycyclic furans.

A representative example of the new reaction is outlined in Scheme 1. The bis-alkynone cycloaddition substrate **1** was conveniently prepared in one step by sequential treatment of commercially available hepta-1,6-diyne with *n*-butyllithium and acetic anhydride. Thermolysis of **1** at 180 °C afforded a product in high yield with spectral characteristics fully consistent with that expected for bicyclic furan **4**; further support for this assignment was subsequently obtained by X-ray analysis of the related product obtained from ynone **7**.

Scheme 1 outlines a likely mechanism to account for the transformation of bis-alkynone **1** to dihydroisobenzofuran **4**. Intramolecular [4 + 2] cycloaddition of **1** produces the strained heterocyclic allene **2,** which undergoes a 1,2-carbon shift to generate carbene intermediate **3**. Insertion of this carbene into an adjacent C−H bond then yields the bicyclic furan product. The intramolecular ynone cycloaddition step proposed in Scheme 1 finds precedent in the related reactions of conjugated enynes,[2,3] which are believed to proceed via the intermediacy of highly strained 1,2,4-cyclohexatrienes.[2,4,5] In these reactions, the isoaromatic intermediates analogous to **2** undergo facile isomerization to form aromatic benzenoid products via radical-mediated and acid-catalyzed pathways. Analogous pathways are not available for **2**, and we believe that the indicated 1,2-carbon shift occurs instead to generate carbene **3** with the simultaneous formation of the aromatic furan ring system. Rearrangements of alkenes to form carbenes are extremely rare, but several examples are known involving bridgehead alkenes,[6] and the well-known interconver-

(1) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.

(2) Danheiser, R. L.; Gould, A. E.; Fernández de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994,** *59,* 5514 and references therein.

(3) For recent examples of enyne cycloaddition reactions, see: (a) Hoffman, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron* **1993,** *49,* 8999. (b) Ionescu, D.; Silverton, J. V.; Dickinson, L. C.; Miller, B. *Tetrahedron Lett.* **1996,** *37,* 1559. (c) González, J. J.; Francesch, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Org. Chem.* **1998,** *63,* 2854.

(4) For early references to cyclic allene intermediates in cycloadditions of conjugated enynes, see: (a) Dykstra, H. B. *J. Am. Chem. Soc.* **1934,** *56,* 1625. (b) Butz, L. W.; Geddis, A. M.; Butz, E. W. J.; Davis, R. E. *J. Org. Chem.* **1940,** *5,* 379.

(5) (a) For a review of cyclic cumulenes, see: Johnson, R. P. *Chem. Rev.* **1989,** *89,* 1111. (b) For evidence for the involvement of cyclic allene intermediates in enyne cycloadditions, see: Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996,** *118,* 4218.

(6) (a) Chan, T. H.; Massuda, D. *J. Am. Chem. Soc.* **1977,** *99,* 936. (b) Barton, T. J.; Yeh, M.-H. *Tetrahedron Lett.* **1987,** *28,* 6421. (c) Eaton, P. E.; White, A. J. *J. Org. Chem.* **1990,** *55,* 1321.

Scheme 1

sion of cycloheptatetraene with phenylcarbene represents a closely related process.[7,8] In the case of **2**, strain in the distorted allene π bond and the generation of an aromatic ring system provide driving force for the rearrangement. Once carbene **3** forms, a facile 1,2-C−H insertion furnishes the dihydroisobenzofuran **4**.

Table 1 outlines the scope of this new synthesis of bicyclic furans. Cycloaddition substrates were conveniently assembled in one to four steps beginning with hepta-1,6-diyne and octa-1,7-diyne using standard acetylide condensation and cross coupling chemistry.[9] Optimal conditions for effecting the reaction involve heating a degassed 0.1 M solution of the diyne in toluene at the indicated temperature for 6−77 h. The addition of the radical inhibitor γ-terpinene was found to improve the efficiency of the reaction, presumably by suppressing polymerization of the ynone starting material.[10]

Electron-deficient alkynes exhibit the greatest reactivity as 2π components ("ynonophiles") in the [4 + 2] ynone cycloaddition. Thus, acetylenes conjugated with carbonyl, aryl, and alkynyl groups undergo reaction at 180 °C, while less activated substrates (e.g., alkynylsilane **9**) require more elevated temperatures. Cycloadditions involving terminal acetylenes as ynonophiles also require reaction temperatures above 200 °C and produce the desired furans in low yield accompanied by multiple byproducts.[11] Among the aryl derivatives **6−8**, the alkyne with an electron-withdrawing *p*-nitrophenyl group reacts 1.3 times faster than the phenylacetylene **6**, and the substrate with a *p*-methoxyphenyl substituent reacts even more slowly to produce the expected bicyclic furan in modest yield. Attempts to employ phenylthioacetylenes as ynonophiles have thus far been unsuccessful. The preference of ynones to combine with *electron-deficient* ynonophiles stands in contrast to the Diels−Alder reactions of α,β-unsaturated carbonyl compounds, where inverse electron demand cycloadditions with electron-rich π bonds generally proceed with the greatest facility.[1]
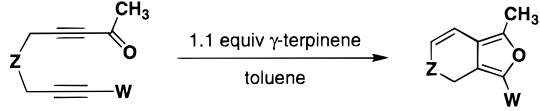
(7) See: Jones, W. M. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, Chapter 3. Wong, M. W.; Wentrup, C. *J. Org. Chem.* **1996,** *61,* 7022. Schreiner, P. R.; Karney, W. L.; Schleyer, P. v. R.; Borden, W. T.; Hamilton, T. P.; Schaefer, H. F. *J. Org. Chem.* **1996,** *61,* 7030 and references therein.

(8) Shevlin has recently reported the generation of thiacyclohexa-2,3,5-triene in the co-condensation of carbon atoms with thiophene and provided evidence that this species undergoes a 1,2-shift of the sulfur atom to produce 2-thiophenylcarbene: Pan, W.; Balci, M.; Shevlin, P. B. *J. Am. Chem. Soc.* **1997,** *119,* 5035.

(9) See Supporting Information for experimental details for the synthesis of the diyne cycloaddition substrates.

(10) Phenolic additives such as BHT were less effective in reducing byproduct formation.

(11) The same bicyclic furan products (i.e., furans lacking a substituent at the carbon derived from the terminal position of the ynonophile) can be readily obtained by protodesilylation of products derived from cycloadditions of alkynylsilanes (e.g., **16** and **17**).

Table 1. Intramolecular [4 + 2] Cycloadditions of Ynones

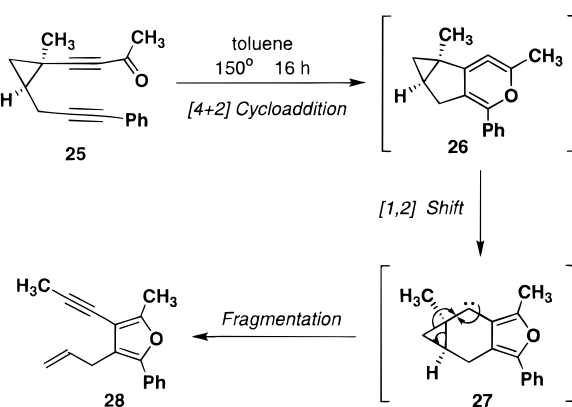| | substrate | | | | |
	Z	W	conditions	product	yield (%)[a]
1	CH$_2$	COCH$_3$	180 °C, 48 h	**4**	80
5	(CH$_2$)$_2$	COCH$_3$	220 °C, 72 h	**12**	20
6	CH$_2$	C$_6$H$_5$	180 °C, 48 h	**13**	70
7	CH$_2$	*p*-(NO$_2$)C$_6$H$_4$	180 °C, 48 h	**14**	81
8	CH$_2$	*p*-(OMe)C$_6$H$_4$	180 °C, 77 h	**15**	58[b]
9	CH$_2$	SiMe$_3$	220 °C, 72 h	**16**	50
10	NTs	SiMe$_3$	111 °C, 14 h	**17**	67
11	CH$_2$	C≡CEt	180 °C, 6 h	**18**	56

[a] Isolated yield. [b] 90% purity by ^{1}H NMR analysis.

As illustrated in Table 1, the length and nature of the tether linking the ynone and ynonophile units also influences the facility of the transformation. When the tether length is increased from three to four carbons, the reaction rate decreases substantially and the desired furan is produced in low yield (compare **1** and **5**). Substitution of an electronegative heteroatom in the connecting chain significantly increases the rate of cycloaddition (e.g., **10** → **17**).

Equation 1 summarizes the results of preliminary experiments probing the relative reactivity of different α,β-alkynyl carbonyl compounds as 4π components in the cycloaddition. In the case of **22** (ester versus ketone), the only product isolated is the ester **23** resulting from exclusive participation of the alkynyl *ketone* moiety as the 4π component in the cycloaddition. All attempts to effect [4 + 2] cycloadditions with α,β-alkynyl aldehydes have thus far been unsuccessful.
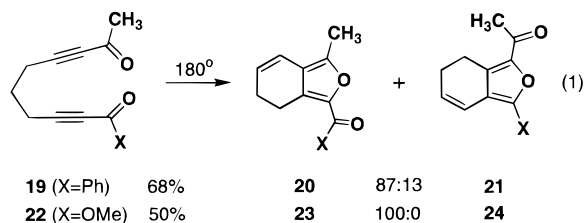
The following experiments provide support for the involvement of heterocyclic allene and carbene intermediates in the mechanism of the ynone cycloaddition reaction. Indirect evidence for heterocyclic allene intermediates of type **2** was easily obtained from flash vacuum thermolysis experiments analogous to those used by Johnson to confirm the intermediacy of strained allenes in the enyne cycloaddition reaction.[5b] However, attempts to obtain evidence for the proposed carbene intermediate **3** through intermolecular trapping experiments have not been successful,

Scheme 2

presumably due to the facility of 1,2-C−H insertion. We therefore undertook the synthesis of cycloaddition substrate **25** (Scheme 2), which we designed with the expectation that the resulting carbene intermediate **27** in this case would undergo a unique fragmentation process leading to **28**.[12] In the event, thermolysis of **25** affords **28** in 30−35% yield, providing strong evidence in support of our proposed mechanism for the ynone cycloaddition reaction.

The dihydroisobenzofuran system generated in the ynone cycloaddition is incorporated as a key structural feature in several classes of natural products, including the viridin family of steroidal antibiotics,[13] and marine pentacyclic quinones such as xestoquinone[14] and halenaquinone[15] which exhibit protein tyrosine kinase inhibitory activity. Further studies are underway in our laboratory to demonstrate the utility of the ynone cycloaddition in the synthesis of these biologically significant compounds and to extend this general cycloaddition strategy to the synthesis of other classes of heterocyclic compounds.

Supporting Information Available: Experimental procedures, X-ray structural information for **14**, and ^{1}H NMR spectra (69 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) For examples of this type of fragmentation process, see: (a) Wheeler, J. W.; Chung, R. H.; Vaishnav, Y. N.; Shroff, C. C. *J. Org. Chem.* **1969**, *34*, 545. (b) Freeman, P. K.; Kuper, D. G. *J. Org. Chem.* **1965**, *30*, 1047.
(13) For a review, see: Hanson, J. R. *Nat. Prod. Rep.* **1995**, 381.
(14) Nakamura, H.; Kobayashi, J.; Kobayashi, M.; Ohizumi, Y.; Hirata, Y. *Chem. Lett.* **1985**, 713.
(15) Roll, D. M.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105*, 6177.