Intramolecular [4 + 2] Cycloaddition Reactions of Conjugated Enynes

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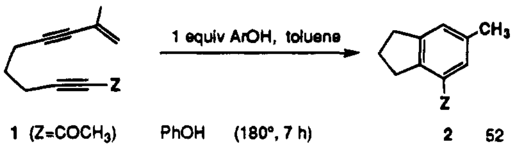
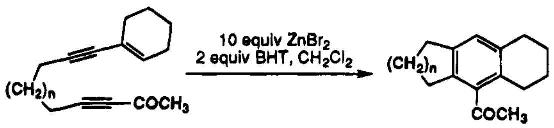
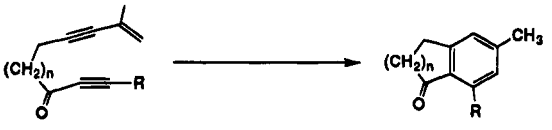
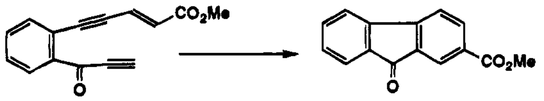
Summary: The intramolecular [4 + 2] cycloaddition of conjugated enynes provides an efficient and general route to aromatic and dihydroaromatic compounds.

The remarkable ability of certain highly unsaturated conjugated systems to undergo thermal cyclization to form new aromatic rings is now well documented.[1] Thus far, however, these unimolecular "cycloaromatizations" have shown little promise as providing the basis for synthetically significant new pathways for ring construction. The goal of our work in this area is the design of *cycloaddition* processes which, like cycloaromatizations, involve highly unsaturated conjugated molecules and proceed via strained and/or high-energy intermediates to afford new aromatic rings and related systems. Herein we report examples of intramolecular [4 + 2] cycloadditions of conjugated enynes, a general process with considerable utility for the synthesis of aromatic and dihydroaromatic compounds.

Table 1 delineates the scope of the enyne cycloaddition reaction. Thermolysis of the acetylenic ketone **1** was examined first, with the expectation that this reaction would lead to the indan **2** via a concerted cycloaddition passing through a strained allene or biradical intermediate (vide infra). In the event, heating a 0.1 M solution of **1** in toluene at 180 °C for 7 h produced the desired cycloaddition product **2** in good yield. Interestingly, the efficiency of this reaction benefited from the presence of phenolic additives, which improved the yield of cycloadduct by ca. 15%, while having little effect on the rate of reaction. As illustrated in Table 1, substrates incorporating electron-deficient alkynes undergo cycloaddition with the greatest facility, consistent with a process influenced by the LUMO energy of the "enynophile" component. Less activated acetylenes react at more elevated temperatures, and among the various substituted acetylenes examined to date, only phenylthio derivatives fail to participate in the reaction.

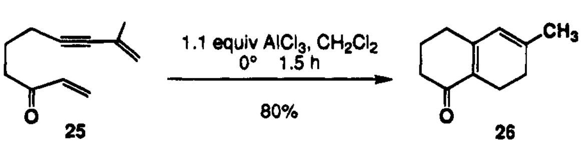
Of particular significance with regard to synthetic utility is the observation that protic and Lewis acids are powerful promoters of the enyne cycloaddition, enabling most reactions to be conducted at or below 0 °C. *Catalytic* amounts of Lewis acids can even be employed, although in these cases extended reaction times and higher temperatures (e.g., 25 °C) are necessary for complete reaction. Also noteworthy is the fact that the reaction proceeds rapidly in the presence of Me_2AlCl, a Lewis acid which can also function as an efficient proton scavenger.[2]

Table 1. Intramolecular Enyne [4 + 2] Cycloadditions

	conditions		yield[a] (%)
	1 equiv ArOH, toluene		
1 ($Z=COCH_3$)	PhOH (180°, 7 h)	**2**	52
3 ($Z=CO_2Me$)	PhOH (180°, 7 h)	**4**	52
5 ($Z=SO_2Ph$)	BHT (180-200°, 7 h)	**6**	77
7 ($Z=SiMe_3$)	p-$MeOC_6H_4OH$ (250°, 36 h)	**8**	48
9 (Z=H)	p-$MeOC_6H_4OH$ (250°, 22 h)	**10**	26[b]
	10 equiv $ZnBr_2$ 2 equiv BHT, CH_2Cl_2		
11 (n=1)	40° 19 h	**12**	76
13 (n=2)	40° 144 h	**14**	71
			
15 (R=H, n=1)	3 equiv BHT, toluene (180°, 16 -18 h)	**16**	68
17 (R=H, n=2)	as above	**18**	78
	2.5 equiv $MeSO_3H$, CH_2Cl_2 (0°, 30 min)		87
	1.1 equiv $AlCl_3$, CH_2Cl_2 (0°, 30 min)		90
	2 equiv Me_2AlCl, CH_2Cl_2 (-78°– rt, 8 h)		49
19 ($R=CH_2OMe$, n=2)	1.1 equiv $AlCl_3$, CH_2Cl_2 (0°, 1.5 h)	**20**	93
21 ($R=CO_2Et$, n=2)	3 equiv $AlCl_3$, CH_2Cl_2 (25°, 1.5 h)	**22**	74
			
23	3 equiv BHT, toluene (110°, 1 h)	**24**	55

[a] Isolated yield of products purified by column chromatography. [b] Product obtained in 35% yield and 75% purity (by ^1H NMR analysis).

As illustrated in eq 1, olefinic enynophiles participate in a variant of the enyne cycloaddition leading to 1,3-cyclohexadienes. The resulting dihydroaromatic products are nicely functionalized for further synthetic elaboration, and this process should find considerable use for the synthesis of six-membered rings. In this regard an important question concerns the stereochemical course of the reaction, an issue currently under active investigation.



25 **26** (1)

Scattered reports have appeared in the previous literature describing transformations related to these intramolecular enyne cycloadditions.[3,4] All of these prior intramolecular reactions involve oxygen in the connecting chain, however, and most are close variants of the dimerization of phenylpropiolic acid[4] involving the intramolecular cycloaddition of an alkyne to an aryl

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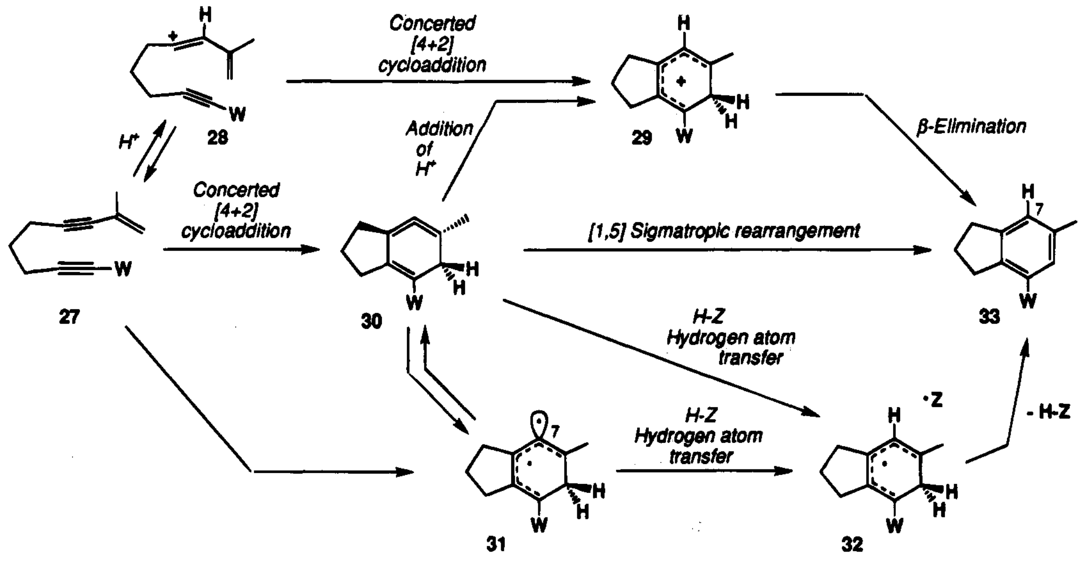
(1) See: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387 and references cited therein.

(2) Snider, B. S.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.

0022-3263/94/1959-5514$04.50/0

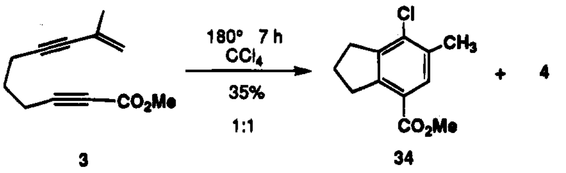
Scheme 1



acetylene. We believe that the examples reported herein demonstrate the generality of the intramolecular enyne cycloaddition for the first time, clearly indicating its potential utility for the synthesis of polycyclic aromatic compounds.

Several possible pathways can be envisaged to account for the mechanistic course of the enyne cycloaddition (Scheme 1; W = electron-withdrawing group). One attractive pathway involves concerted [4 + 2] cycloaddition to generate the isoaromatic 1,2,4-cyclohexatriene **30**, which may be in equilibrium with biradical **31**.[5-7] Alternatively, **27** could undergo cyclization to afford the biradical **31** directly. The presence of acid introduces a third pathway for ring formation: generation of butadienyl cation **28**, followed by [4 + 2] cycloaddition to produce the delocalized carbocation **29**.[8] Alternatively, Lewis acids may simply activate **27** and lower the barrier for cycloaddition to the cyclic allene. As shown in Scheme 1, several mechanisms can be envisioned for the isomerization of these various intermediates to the indan product **33**. The possibility that multiple pathways may operate in these reactions (depending on reaction conditions and substrate structure) cannot be excluded.

Studies are currently underway in our laboratory to elucidate the mechanism of these intriguing reactions. Two of our initial observations deserve note. First, we have found that the rate of the thermal cycloaddition of **17** in C_6D_6 (0.05 M, 180 °C) is unaffected by the addition of acid scavengers such as 2,6-di-*tert*-butyl-4-methylpyridine. In addition, thermolysis of **3** in CCl_4 produced a mixture of **4** and the byproduct **34** incorporating chlorine



(2)

at C-7. For at least the thermal version of the enyne cycloaddition, these results and the other data presented here are consistent with a concerted pathway involving the intermediacy of the biradical **31**, possibly derived from cyclic allene **30**.

Finally, it should be noted that although the direct cycloaddition of an enyne to form a highly strained cyclic allene such as **30** might appear to be an energetically unfavorable process, in fact we estimate the enthalpy of reaction for this transformation to be −29.7 kcal/mol.[9] The exothermicity of this process no doubt benefits from the highly favorable translation of relatively weak acetylenic π bonds into two new carbon−carbon σ bonds. Further studies are underway in our laboratory to exploit this principle in the design of other useful ring-forming strategies.

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Supplementary Material Available: Experimental procedures and full characterization for all cycloaddition reactions (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(3) (a) Johnson, A. W. *J. Chem. Soc.* **1945**, 715. (b) Nazarov, I. N.; Verkholetova, G. P.; Torgov, I. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1959**, *29*, 3277. (c) Hakopian, L. A.; Gesalian, G. I.; Grigorian, S. G.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, *27*, 764. (d) Hakopian, L. A.; Gezalian, G. I.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, *27*, 768. (e) Hoffmann, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron* **1993**, *49*, 8999.

(4) (a) Michael, A.; Bucher, J. E. *Chem. Ber.* **1895**, *28*, 2511. (b) Michael, A.; Bucher, J. E. *Am. Chem. J.* **1898**, *20*, 89. For later developments see: (c) Haworth, R. D.; Kelly, W. *J. Chem. Soc.* **1936**, 745. (d) Baddar, F. G.; El-Assal, L. S.; Doss, N. A. *J. Chem. Soc.* **1959**, 1027. (e) Brown, D.; Stevenson, R. *J. Org. Chem.* **1965**, *30*, 1759. (f) Cadby, P. A.; Hearn, M. T. W.; Ward, A. D. *Aust. J. Chem.* **1973**, *26*, 557 and references cited therein.

(5) For a theoretical study of 1,2,4-cyclohexatriene, see: Janoschek, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 476.

(6) Generation and trapping of isoaromatic systems: (a) Miller, B.; Shi, X. *J. Am. Chem. Soc.* **1987**, *109*, 578. (b) Christl, M.; Braun, M.; Müller, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 473. (c) For a review of cyclic cumulenes, see Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111.

(7) To our knowledge, the first reference to a cyclic allene intermediate in the context of an enyne cycloaddition should be credited to Butz; see: Butz, L. W.; Geddis, A. M.; Butz, E. W. J.; Davis, R. E. *J. Org. Chem.* **1940**, *5*, 379.

(8) Nazarov appears to be the first to have discussed the butadienyl cation pathway, a mechanism which he suggested in connection with his study of the acid-promoted dimerization of vinylethynylcarbinols.[3b] For other discussions of the butadien-1-yl cation [4 + 2] cycloaddition mechanism, see ref 3e and: Whitlock, H. W., Jr.; Wu, E. M.; Whitlock, B. J. *J. Org. Chem.* **1969**, *34*, 1857.

(9) Estimated using the Benson group additivity method (Benson, S. W. *Thermochemical Kinetics*; Wiley: New York, 1976) and the calculated[5] heat of formation for 1,2,4-cyclohexatriene (93.7 kcal/mol).