Approaches to the Synthesis of Strained Cycloalkynes

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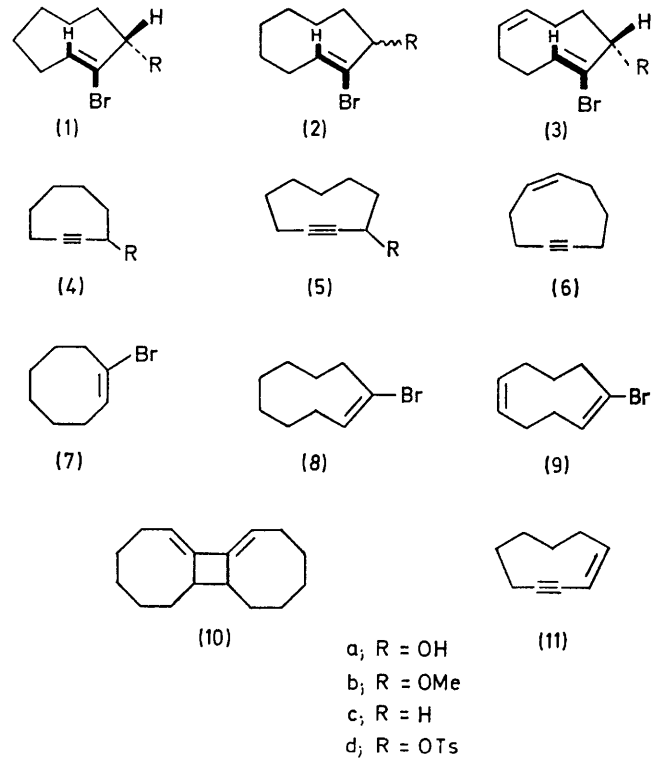
Summary Convenient procedures for the synthesis of cyclononyne (**5c**) and cyclonon-1-en-5-yne (**6**) are described; the preparation of cyclonon-1-en-3-yne (**11**) is also reported.

WE recently described[1,2] procedures for the preparation, in virtually quantitative yields, of *trans*-2-bromocyclo-octen-3-ol (**1a**), *trans*-2-bromocyclononen-3-ol (**2a**), *trans,cis*-2-bromocyclonona-1,6-dien-3-ol (**3a**), and their methyl ethers (**1b**, **2b**, and **3b**, respectively). We have also demonstrated[3] that when such *trans*-2-bromocycloalkene derivatives are treated with potassium t-butoxide in dimethyl sulphoxide for 5 s at 20°, high yields of the corresponding 3-substituted cycloalkynes are usually obtained.† Thus 3-methoxycyclo-octyne (**4b**) was obtained[3] as a pure liquid, in 74% isolated yield, from (**1b**). As this procedure compares favourably, both from the standpoints of convenience and yields obtained, with the other procedures described[4] for the synthesis of strained cycloalkynes, attempts were made to utilize it in the preparation of the parent hydrocarbons (**4c**, **5c**, and **6**).

Reaction between *trans*-2-bromocyclo-octen-3-ol[1] (**1a**) and toluene-*p*-sulphonyl chloride in pyridine gave the toluene-*p*-sulphonate ester (**1d**) in modest yield. When the latter compound was treated with an excess of lithium aluminium hydride in ether at 0°, a good yield of *cis*-1-bromocyclo-octene (**7**) was obtained. None of the desired *trans*-isomer (**1c**) was detected in the products. This result is noteworthy as the *trans*-isomer (**1c**) is the expected product if the lithium aluminium hydride reduction of (**1d**) proceeds either by an S_N2 or an S_N2' reaction.[5] However, treatment of the toluene-*p*-sulphonate ester (**2d**) of *trans*-2-bromocyclononen-3-ol[1] with lithium aluminium hydride under the same conditions gave a good yield of a mixture of 1-bromocyclononenes which consisted of *ca.* 60% of *cis*-



† It may be desirable or necessary to protect the OH function of a *trans*-2-bromocycloalken-3-ol by tetrahydropyranylation before attempting to convert it into the corresponding cycloalkyn-3-ol. Such protection is necessary in the preparation[3] of cyclo-octyn-3-ol (**4a**) but not of cyclononyn-3-ol (**5a**).

isomer (**8**) and *ca.* 40% of *trans*-isomer (**2c**). As the overall yield of the latter compound (**2c**) was below 20%, based on the alcohol (**2a**) as starting material, this approach to the synthesis of cyclononyne (**5c**) did not appear to be promising.

A more satisfactory result was obtained in the preparation of *trans,cis*-1-bromocyclonona-1,5-diene (**3c**). Thus the *cis,cis*-isomer (**9**) could not be detected in the lithium aluminium hydride reduction products of the appropriate toluene-*p*-sulphonate ester (**3d**) and pure (**3c**) was isolated from these products in 75% overall yield, based on the corresponding alcohol (**3a**) as starting material. Treatment of (**3c**) with $KOBu^t$–Me_2SO under the usual conditions[3] (see above) gave cyclonon-1-en-5-yne (**6**) which was isolated as a pure colourless liquid, b.p. 86—90°/35 mm, in 67% yield.

The other obvious approach to the problem was to attempt to convert the cycloalkyn-3-ols (**4a** and **5a**) into the corresponding cycloalkynes (**4c** and **5c**). Treatment of cyclo-octyn-3-ol[3] (**4a**) with methanesulphonyl chloride and triethylamine in dichloromethane gave its methanesulphonate ester[6] (**4**; R = OSO_2Me). When the latter compound was treated with lithium aluminium hydride in ether at 5°, no cyclo-octyne (**4c**) but a good yield of (**10**), the dimer of cyclo-octa-1,2-diene,[7] was obtained. This result suggests that lithium aluminium hydride reduction of (**4**; R = OSO_2Me) proceeds by an S_N2' mechanism. However, reduction of 3-mesyloxycyclononyne (**5**; R = OSO_2Me) with lithium aluminium hydride gave mainly cyclononyne (**5c**). The crude products contained a small amount of the isomeric cyclonona-1,2-diene but pure cyclononyne (**5c**) was isolated in 35% overall yield for the four steps starting from 9,9-dibromobicyclo[6,1,0]nonane, the precursor of (**2a**). This would appear to be the method of choice for the preparation of cyclononyne (**5c**), but it has, so far, only been used to obtain relatively small (*ca.* 1·5 g) quantities of it.

Finally, attempts are being made to use the available functionalized 2-bromo-*trans*-cycloalkenes and cycloalkynes as intermediates in the preparation of the corresponding conjugated en-ynes. In a preliminary experiment, cyclonon-1-en-3-yne (**11**) was obtained in modest yield from the products of the reaction between $KOBu^t$ and 3-bromocyclononyne (**5**; R = Br) in t-butyl alcohol. 3-Bromocyclononyne was readily obtained by the action of triphenylphosphine dibromide[8] on cyclononyn-3-ol[3] (**5a**) in acetonitrile.

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[1] C. B. Reese and A. Shaw, *J. Amer. Chem. Soc.*, 1970, **92**, 2566.
[2] C. B. Reese and A. Shaw, *Chem. Comm.*, 1970, 1365.
[3] C. B. Reese and A. Shaw, *Chem. Comm.*, 1970, 1172.
[4] For a review of synthetic methods, see A. Krebs in 'Chemistry of Acetylenes,' ed. H. G. Viehe, Dekker, New York, 1969, pp. 998—1005.
[5] G. H. Whitham and M. Wright, *J. Chem. Soc.* (*C*), 1971, 891.
[6] R. K. Crossland and K. L. Servis, *J. Org. Chem.*, 1970, **35**, 3195.
[7] E. T. Marquis and P. D. Gardner, *Tetrahedron Letters*, 1966, 2793.
[8] L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 1247.