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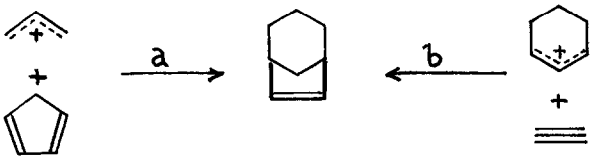
BICYCLO[3.2.1]OCT-6-ENES via (3+2)CYCLOADDITION

Brian D. Gray[a], Catherine M. McMillan, J. Allen Miller*[b], and Michael Moore,
Department of Chemistry, The University, Dundee DD1 4HN, Scotland, U.K.

ABSTRACT (3+2)Cycloaddition of alkynes to allyl cations, generated from 3-chlorocyclohexenes and zinc chloride, provides a simple and direct route to bicyclo[3.2.1]oct-6-enes.

Bicyclo[3.2.1]octane derivatives are of interest because of their occurrence in natural product structures, many of which are of biological[1] or medicinal[2] consequence, and because this relatatively rigid ring system permits the study of stereochemical aspects of structure and reactivity.[3] Despite this interest, synthetic routes to this ring system are not numerous, and many are of limited application, and not appropriate to the synthesis of simple derivatives of the bicyclo[3.2.1]octane family.[4] Recent work by several groups has improved this situation somewhat, with reports of novel cyclisations[5] and rearrangements[4,6] leading to bicyclo[3.2.1]octanes.

However, the most direct route to bicyclo[3.2.1]octanes from simple starting materials is via cycloaddition. Two basic modes of cycloaddition may be perceived, as illustrated below for the preparation of bicyclo[3.2.1]oct-6-enes from allyl cation precursors.

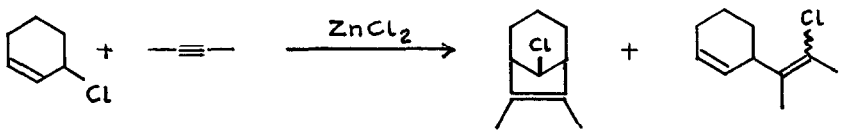


Reaction type a has been described by other groups,[7] although it has been applied more generally to heterocyclic variants, using furan or certain pyrroles as dienes.[8] Previous work from our laboratory has demonstrated the feasibility of reactions of type b for the synthesis of cyclopentenes, via (3+2)cycloaddition (where the terminology has only a

a Present address: Smith Kline and French Laboratories,
709 Swedeland Rd, Swedeland, PA 19479, U.S.A.

b Present address: Department of Medicinal Chemistry, Wellcome Research Laboratories, Beckenham, Kent. BR3 3BS, England.

structural, but no mechanistic significance). We now report that bicyclo[3.2.1] oct-6-enes are also accessible by this methodology. A structurally related sequence has been described for 8-oxabicyclo[3.2.1]octanes, via addition of 3-oxidopyrilium ylids to alkenes.[10] The key step in our synthesis requires interaction of a Lewis acid with an allylic halide in the presence of an alkyne, which is the two carbon component of the cycloaddition. Typically the catalyst is commercial powdered zinc chloride (~2 mol. equiv.), the solvent is dichloromethane, and reaction achieved by gradual addition of a solution of the allyl halide to a stirred suspension of the catalyst in a solution of the alkyne, followed by stirring of the mixture for 1-3 h, in the temperature range -30-20°C. The cycloadduct, (1), is frequently accompanied by an isomer, (2), resulting from simple addition of the allylic halide across the alkyne, and careful chromatography (dry column or flash) is normally required to separate the two products. Examples and yields are given in the Table, and the general reaction illustrated by the equation.



(1) (2)

The cycloaddition has a number of regio- and stereochemical features worthy of emphasis. Firstly,the bridge halogen, normally chlorine, is always sited axially in the cyclohexane ring (i.e. exo to the cyclopentene ring), as revealed routinely by vincinal coupling (J 5Hz) to the bridgehead hydrogen(s). In cases where two regioisomers may form across the new bonds, only one isomer is normally observed, as in entries 1-6, 9 and 11 in the Table. Further subtleties of stereochemistry are observed in cycloadducts with substituents at C-3 or C-4 of the bicyclo[3.2.1]octene. Thus a 3-phenyl group has solely an equatorial placement (entry 13), whilst a 4-methyl group usually has a preference for an axial orientation (entries 9, 10 and 13). These features clearly reflect mechanistic nuances which appear to be general for (3+2)cycloaddition reactions of this type, and therefore can be used predictively in synthetic situations.

Another potentially valuable aspect of the cycloaddition is that it generates two reactive, but readily distinguishable, functionalities within a rigid framework. Stereospecific transformations at the bridge and at the double bond have been found to be facile and will be described in detail elsewhere. Added to these features, the ready accessibility of the reactants, the mild conditions and the simple procedure should make this method a valuable synthetic entry to bridged bicyclics of the [n.2.1]type.

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TABLE (3+2)cycloaddition reactants and bicyclic products

Entry	Reactants[a,b]		Products[a,c]	% yield (exo:endo isomer ratio)
1	R^1_5=Me (5) and R^5=Me (1)	R^7Ph, R^6=Me	R^1_7=R^6=Me; R^7=Ph	51
2	"	R^7=Ph,R^6=H	R^1=Me, R^7=Ph	20
3	"	R^7=Ph, R^6=CH_2OMe	R^1_7=Me,R^6=CH_2OMe R^7=Ph	47
4	R^1=R^3=R^4=R^5=H	R^7=Ph,R^6=Me	R^6=Me; R^7=Ph	58
5	"	R^7=Ph,R^6=Me	R^6=Me; R^7=Ph	76[d]
6	"	R^7=Ph,R^6=H	R^7=Ph	21
7	"	R^7=R^6=Et	R^6=R^7=Et	74
8	R^1_5=Ph (88) and R^5=Ph (9)	R^7=R^6=Et	R^1=Ph,R^6=R^7=Et	39
9	R^1=Me, R^4= Me	R^7=Ph,R^6=Me	R^1_7=R^4=R^6=Me R^7=Ph	82 (2:1)
10	"	R^7=R^6=Ph	R^1_6=R^4_7=Me R^6=R^7=Ph	38 (4:1)
11	"	R^7=Ph, R^6=H	R^1_7=R^4=Me R^7=Ph	48 (1:2)
12	"	R^7=R^6=Et	R^1_6=R^4_7=Me R^6=R^7=Et	30 (4:1)
13	R^1_3=Me,R^3=$_5$Ph (78) and R^3= Ph, R^5=Me (11)	R^7=R^6=Et	R^1_6=Me;$_7R^3$=Ph R^6 = R^7 = Et	53 (all exo)

[a] Substituents denoted by R are hydrogen except where stated otherwise

[b] Figures in parenthesis indicate isomeric ratio (nmr) of allyl chloride mixtures

[c] Products are racemic, but represented as one enantiomer only

[d] Reaction performed in carbon tetrachloride medium

References

1. Examples include the trichothecenes, gibberellins, helminthosporanes and some lignans

2. Examples include aphidicolin (anti-tumour agent), adenanthin (anti-tumour agent), secoishwaran-12-ol (antifertility agent).

3. For example, see H. Maskell and A. A. Wilson, J. Chem. Soc., Perkin Trans. II, 1982, 39; W.N. Washburn, J. Org. Chem., 1983, 48, 4287; E. Kaufmann, H. Mayr, J. Chandrasekhar, and P. R. Schleyer, J. Am. Chem. Soc., 1981, 103, 1375.

4. A number of authors remark on this situation, e.g. A. J. Barker, M. J. Begley, M. Mellor, D. A. Ofieno, and G. Pattenden, J. Chem. Soc., Perkin Trans I, 1983, 1893; G. A. Kraus, Y.-S. Hon, and J. Sy, J. Org. Chem., 1986, 51, 2625.

5. R. L. Funk, L. H. M. Horcher, J. V. Daggett, and M. M. Hansen, J. Org. Chem., 1983, 48, 2632; A. J. Pearson, Tetrahedron Lett., 1980, 21, 3929; A. S. Kende, B. Roth, and P. J. Sanfilippo, J. Am.Chem. Soc., 1982, 104, 1784; G. Majetich, R. W. Desmond, and J. J. Soria, J. Org. Chem., 1986, 51, 1753; also see A. B. Smith and R. K. Dieter, Tetrahedron, 1981, 37, 2407, for a review of α-diazoketone cyclisation, notably the work of the groups led by Ghatak and by Mander.

6. E. Piers, G. L. Jung, and N. Moss, Tetrahedron Lett., 1984, 25, 3959; R. Dasgupta, P. R. Kanjilal, S. K. Patra, M,. Sarkar, and U. R. Ghatak, Tetrahedron, 1985, 41, 5619; M. Fetizon, D. D. Khac, and N. D. Tho, Tetrahedron Lett., 1986, 27, 1777; P. B. Anzeveno, D. P. Matthew, C. L. Barney, and R. J. Barbuck, J. Org. Chem., 1984, 49, 3134; W. M. Grootaert, and P. J. De Clercq, Tetrahedron Lett., 1986, 27, 1731.

7. N. Shimizu, M. Tanaka, and Y. T. Tsuno, J. Am. Chem. Soc., 1982, 104, 1330; T. Sasaki, Y. Ishibashi, and M. Ohno, Tetrahedron Lett., 1982, 23, 1693; D. I. Rawson, B. K. Carpenter, and H. M. R. Hoffmann, J. Am. Chem. Soc., 1979, 101, 1786; H. M. R. Hoffmann, and M. N. Igbal, ibid, 1972, 94, 3940.

8. B. Föhlisch, E. Gehrlach, and R. Herber, Angew. Chem. Suppl., 1982, 241-249; B. Föhlisch, W. Gottstein, R. Kaiser, and I. Wanner, Tetrahedron Lett., 1980, 21, 3005; A. P. Cowling, J. Mann, and A. A. Usmani, J. Chem. Soc., Perkin Trans. I, 1981, 2116; J. Mann and H. J. Overton, Tetrahedron Lett., 1985, 26, 6133; T. Sato, H. Kobayashi, and R. Noyori, ibid, 1980, 21, 1971.

9. J. A. Miller and M. Moore, Tetrahedron Lett., 1980, 21, 577.

10. P. G. Sammes, L. J. Street, and P. Kirby, J. Chem. Soc., Perkin Trans. I, 1983, 2729; P. G. Sammes and L. J. Street, J. Chem. Research (S), 1984, 196; J. B. Hendrickson and J. S. Farina, J. Org. Chem., 1980, 45, 3359.

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