

RING CLOSURES VIA THE WURTZ REACTION

A CONVENIENT SYNTHESIS OF CYCLOBUTANE

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Although the Wurtz reaction has previously been used in the synthesis of a few alicyclic compounds, practical considerations such as yields, accessibility of starting materials, and the availability of good alternative routes have severely limited its use. Indeed, its utility has been almost exclusively limited to the closures of three membered rings, the best example being the synthesis of cyclopropane in greater than 80% yield (1). Other examples include the synthesis of spiro[2.5]octane (2) (58% yield) and the synthesis of spiro[2.4]heptane (3) (79% yield) from pentaerythrityl tetrabromide with the use of tetrasodium ethylenediaminetetraacetate to remove zinc bromide as it was formed. (Zinc bromide, a Lewis acid, apparently rearranges the intermediate dibromide leading ultimately to the formation of methylene cyclobutane.) A successful Wurtz synthesis of cyclobutane eluded chemists for more than a half a century (4). It was finally prepared in 7% yield from the action of sodium in refluxing toluene upon 1,4-dibromobutane (5) and later in 20% yield by the use of lithium metal in refluxing ether (6). Recently bicyclo[1.1.0]butane has been synthesized by the treatment of 1,3-dibromocyclobutane with sodium metal in refluxing dioxane (7). Similarly bicyclo[1.1.1]pentane has been synthesized by the treatment of 3-(bromomethyl)-cyclobutyl bromide with sodium metal although in only a 0.5% yield (8). By the use of lithium amalgam in refluxing dioxane it was possible to raise this yield to 4.2% and preliminary results indicated the mono-radical-anion derived from sodium/naphthalene gave an 8% yield (8). The present work outlines some of the scope and limitations of these reagents.

Table I summarizes the results obtained in the synthesis of cycloalkanes from a number of dihaloalkanes and bases in various solvents under a variety of reaction conditions. Under the best conditions found the reaction of 1,4-dibromobutane with lithium amalgam in refluxing

TABLE I
Wurtz Closure of 1,4-Dihalalkanes to Cycloalkanes a)

Halide	Base	Solvent	Temp. °C.	Product	% Yield b) 3 hrs. 24 hrs.	% Halide c) Removal
$\text{Br}(\text{CH}_2)_4\text{Br}$	Li/Hg	Dioxane	101	Cyclobutane	70	
"	"	"	80	"	29 48	
"	"	THF	66	"	64	100
"	"	"	25 d)	"	39-43	85
"	"	Et_2O	25 d)	"	1.9	
"	$\text{Na}/\text{naphthalene}$	1,2-Dimethoxyethane	25-35	"	25 e)	
"	"	"	0	"	12 e)	
$\text{Br}(\text{CH}_2)_4\text{Cl}$	Li/Hg	Dioxane	101	"	35 57	
"	"	THF	66	"	19 38	
$\text{Cl}(\text{CH}_2)_4\text{Cl}$	"	Dioxane	101	"	26	47
"	"	THF	66	"	32	68
$\text{Br}(\text{CH}_2)_5\text{Br}$	"	Dioxane	101	Cyclopentane	76	
"	"	Et_2O	25 d)	"	Trace	
"	"	"	35	"	31	93
$\text{Br}(\text{CH}_2)_{10}\text{Br}$	"	THF	66	Cyclodecane	.05	76

a) For experimental procedures see reference 8.

c) Percent halide removed was determined as a measure of the amount of organo halide reacted.

b) Yields of cyclobutane and cyclopentane are based on weighed, chromatographed product.

d) Product-solvent mixture was distilled from the reagent at 200 mm. Hg. at end of reaction.

e) Quenched with methanol before distillation of the cyclobutane.

dioxane gives cyclobutane in a 70% yield. This is a tenfold increase over the best reported yield with sodium metal and provides the first practical one-step synthesis of cyclobutane from commercially available starting material. Moreover, in all cases the volatile material is 99% pure cyclobutane. These high yields of essentially pure cyclobutane are in sharp contrast to the results obtained in a study of the reaction of various alkali and alkaline earth metals upon 1,4-dibromobutane. For example, sodium metal in refluxing xylene gave volatile hydrocarbon mixtures containing 63% ethylene, 16% butane, 5% 1-butene, 2% 2-butene, 3% butadiene and 11% cyclobutane (9).

For products stable to 100° dioxane would appear to be the solvent of choice although only slightly reduced yields are obtained with tetrahydrofuran at 66°; yields which are better than those obtained with dioxane at the same lower temperature. Diethyl ether does not appear to be a suitable solvent.

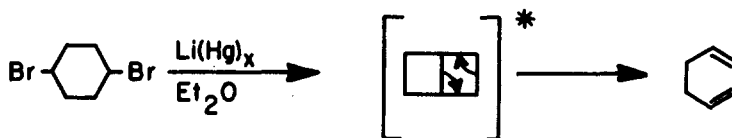
Since the aromatic mono-radical-anion derived from sodium and naphthalene has been successful (8% yield) in the preparation of bicyclo[1.1.1]pentane (8) as well as in the preparation of normal alkanes such as decane (50% yield) (10), this reagent was tried with 1,4-dibromobutane in 1,2-dimethoxyethane as solvent. The 25% yield of cyclobutane at 25-30° and the 12% yield at 0° suggest the use of these conditions for thermally instable products although it should be mentioned that a large part of the volatile material from the reaction is methyl vinyl ether, the cleavage product of 1,2-dimethoxyethane.

As might be expected, replacing bromine by chlorine slowed the reaction rate, increasing the chain length to give cyclopentane increased the yield slightly and increasing the chain length to 10 methylene units dropped the yield to 0.05% (based upon the NMR integral of fractions boiling at 40-74°/1-4 mm. Hg). The other products (~90 to 95%) were the results of intermolecular coupling (average: trimer) with traces of reduction and elimination (methyl and terminal olefin signals in the NMR spectra).

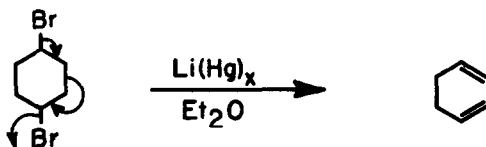
Finally the action of lithium amalgam on a mixture of 1,3- and 1,4-dibromocyclohexane was studied. This mixture was prepared by the action of hydrobromic acid upon 1,3-cyclohexanediol and is 32.6% trans-1,3-, 30.9% trans-1,4-, 21.9% cis-1,3-, and 14.6% cis-1,4-dibromocyclohexane according to the literature (11). This mixture was stirred with lithium amalgam in ether for 5 days, after which it was worked-up by filtering, washing the ether layer with water, and removing the ether at room temperature. At no time was it heated to the rearrangement temperature of bicyclo[2.2.0]hexane (12). Although 47.5% of the bromine had been removed, yields of

only 12.2% bicyclo[3.1.0]hexane, and 7.1% 1,5-hexadiene were found. If it is assumed that no rearrangement of the equilibrium mixture occurred during the reaction, transannular coupling of the cis-trans mixture of 1,3-dibromides has occurred to the extent of 22.4%.

The absence of bicyclo[2.2.0]hexane may be explained in two ways. First, it is possible that the geometry of the cis and trans-1,4-dibromocyclohexanes is unfavorable. In other words the internuclear distance (1,4) may be too great in the rather rigid cyclohexane ring, whereas the 1,4-dihalobutanes may possess enough more flexibility to account for the high yields of cyclobutane obtained. Second, it is possible that the initially-formed bicyclo[2.2.0]hexane possesses sufficient energy to fragment since the activation energy for this fragmentation has been shown to be low (12) and this would account for the formation of 1,5-hexadiene.



However, 1,5-hexadiene might also arise from a direct fragmentation of 1,4-dibromocyclohexane:



(Note that the above mechanism is depicted as being ionic for the sake of graphic convenience only; similarly, a radical mechanism may also be drawn.)

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