

REACTION OF α,ω -DIODIDES WITH *t*-BUTYLLITHIUM. FACILE ROUTE TO
THREE-, FOUR- AND FIVE-MEMBERED CYCLOALKANES

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Abstract. Carbocyclic three-, four- and five-membered rings are formed in good to excellent yield (87-100%) upon treatment of the appropriate α,ω -diiodide with *t*-butyllithium in pentane-ether solution at -23°C. The corresponding dibromides do not undergo clean cyclization.

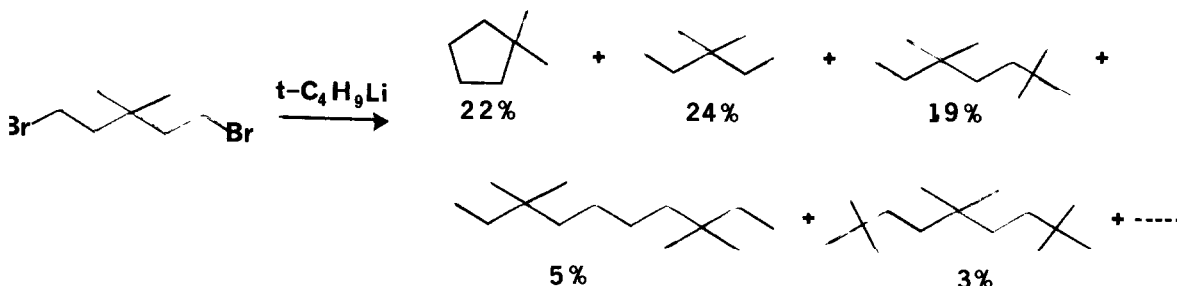
The construction of unfunctionalized carbocyclic rings by reductive cyclization of α,ω -dihalides has been attempted with mixed success using a variety of reducing agents. In general, while 1,3-dihalides are easily converted to cyclopropanes in high yield,² 1,4-dihalides give quite variable yields of cyclobutanes³ and, with a few notable exceptions,⁴ the cyclization of longer chain dihalides is not a viable route to larger carbocycles.

A conceptually simple route to cycloalkanes involves treatment of an α,ω -dihalide with an alkylolithium.⁵ In a formal sense this mechanistically intriguing process may be viewed as an intramolecular Wurtz-type coupling of an α -lithio- ω -haloalkane formed by initial metal-halogen interchange.⁶ Although such an approach has been exploited by Parham, Bradsher and co-workers for the preparation of benzocyclobutenes and indans from (bromophenyl)alkyl halides,⁷ a plethora of competing reactions (*v.e.*, intermolecular coupling, reduction, elimination, *etc.*)^{5,6} seriously compromise the method as a general route to cycloalkanes.^{2,3}

During the course of an investigation of the metal-halogen interchange reactions we reexplored the use of alkylolithiums as reagents for cyclization of α,ω -dihalides. We have found that reductive cyclization is virtually the exclusive route followed when *primary* 1,3-, 1,4- or 1,5-diodides are treated with *t*-butyllithium in pentane-ether solution at -23°C. As shown in Table 1, side reactions are suppressed and good to excellent yields of three-, four- and five-membered carbocyclic rings are routinely obtained when diiodides are used as substrates. The corresponding dibromides, however, do not undergo clean intramolecular cyclization under these conditions.

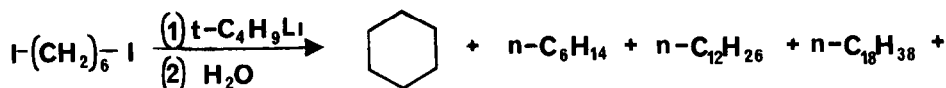
The disparate behavior of diiodides and dibromides in reactions with *t*-butyllithium is striking. For example, whereas 3,3-dimethyl-1,5-diodopentane was cleanly converted to 1,1-dimethylcyclopentane upon treatment with *t*-butyllithium (Table 1), the analogous dibromide afforded a complex mixture of hydrocarbons containing only a minor amount of the carbocycle. The use of other dibromides in place of the diiodides listed in Table 1 resulted in the formation of similar product mixtures. It is of some interest to note that a substantial proportion of the product (~20-25%) from reaction of a dibromide with *t*-butyllithium is formally derived

via Wurtz-type coupling of the alkyllithium with the substrate. Moreover, the proportion of these "mixed-Wurtz" products is virtually unaffected by running the reactions at higher dilution.¹





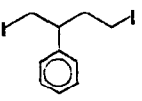

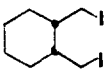

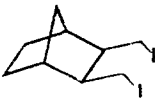
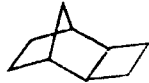


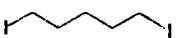



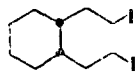
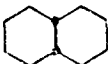
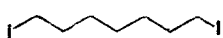

The fact that dibromides behave in a qualitatively different manner than diiodides⁸ has a bearing on the much debated mechanism for metal-halogen interchange^{5,6} since it suggests that there is a halogen effect in the interchange process. This observation, which will be explored in the full account of our investigation, is inconsistent with any mechanism for metal-halogen interchange that does not include the departing halogen in the product-partitioning step.⁹

Reductive cyclization of diiodides does not provide a practical route to carbocycles larger than cyclopentanes. Treatment of 1,6- or 1,7-diiodides with *t*-butyllithium produces little cycloalkane (*ca* 0-25%, Table 1)¹⁰ The major products, as shown below for the case of 1,6-diiodohexane, are *n*-alkanes derived from reduction of the diiodides (presumably *via* α,ω -dilithio species) along with smaller quantities of saturated hydrocarbons derived from intermolecular coupling of substrate molecules. Virtually no mixed coupling of diiodide with *t*-butyllithium was observed in any of the reactions and, as expected, the extent of dimer, trimer, *etc.* formation could be decreased by lowering the initial concentration of the diiodide in the reaction mixture.



The general method employed for cyclization of α,ω -diiodides is as follows. A solution of the diiodide (10 mmol) in dry pentane-ether (100 ml, 3:2 by volume) was cooled to -23°C (CCl_4/CO_2 bath) under a blanket of argon and 2.0 to 2.2 molar equivalent¹¹ of commercial *t*-butyllithium was added *via* syringe. After stirring for 30 min at -23°C (during which time a white ppt forms), the reaction mixture was allowed to warm to room temperature, 10 ml of water was cautiously added and the hydrocarbon products were isolated or assayed by standard methods.

Table 1. Conversion of α,ω -Diodides to Cycloalkanes

Diodide	Cycloalkane	Yield, ^{a,b} %
		93
		87 (78)
		97
		99 (52)
		93
		98
		5
		16
		~0

^a Absolute yields determined by glc analysis of the reaction mixture and correction for detector response

^b Isolated yields in parenthesis

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References and Notes

- 1 Taken in part from the Ph.D. Dissertation of R Paul Gagnier, University of Connecticut, Storrs, CT, 1981.
- 2 The literature relating to cyclization of 1,3- and 1,4-dihalides has been reviewed in the Houben-Weyl series. For cyclopropanes, see. Wendisch, D. in *Methoden der Organischen Chemie*, George Thieme Verlag: Stuttgart, 1971; Vol. 4, pt. 3. For cyclobutanes, see. Seebach, D *ibid.*, Vol. 4, pt. 4.
3. (a) Conner, D. S., Wilson, E. R., *Tetrahedron Lett.* 1967, 4925.
(b) Wiberg, K B., Epling, G. A., *ibid.*, 1974, 1119
4. (a) Takahashi, S., Suzuki, Y., Hagihara, N., *Chem. Lett.* 1974, 1363.
(b) Whitesides, G M., Gutowski, F. D., *J. Org. Chem.* 1976, 41, 2882.
5. (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*, Pergamon Press New York, 1974.
(b) Schöllkopf, U. in *Methoden der Organischen Chemie* (Houben-Weyl); George Thieme Verlag: Stuttgart, 1970, Vol. 13, pt. 1.
6. Gilman, H., Jones, R. G. *Organic Reactions*, Wiley: New York, 1951, Vol VI, Chpt. 7.
- 7 (a) Parham, W. E., Jones, L. D , Sayed, Y A., *J. Org. Chem.* 1976, 41, 1184.
(b) Parham, W. E., Bradsher, C. K., Reames, D C., *ibid.*, 1981, 46, 4804
8. Differences in behavior of RBr and RI when treated with RL₁ have been noted by Applequist, D. E., O'Brien, D. F *J. Amer. Chem. Soc.* 1963, 85, 743.
- 9 Halogen effects have been observed in reactions of RX with disodium tetraphenylethylene and radical anions have been implicated as intermediates in these interchange processes Cf. Garst, J F., Roberts, R D., Pacifico, J. A *J. Amer. Chem. Soc.* 1977, 99, 3528.
10. The precipitous drop in yield of cycloalkane at a chain length of six-atoms is not unexpected. A similar observation was made by Garst and Barbas in their elegant pioneering study of the reactions of α,ω -dihalides with alkali naphthalenes [Garst, J F, Barbas, J. T *J. Amer. Chem. Soc.* 1974, 96, 3239 and 3247] In this connection, it is to be noted that, although 1,4- and 1,5-dihalides are reductively cyclized upon treatment with alkali naphthalenes, the yield of cycloalkanes is moderate (ca. 40-60%) and significant amounts of alkylated naphthalenes are produced
- 11 One equivalent of the *t*-butyllithium is consumed by reaction with the *t*-butyl iodide generated in the metal-halogen interchange. Cf. Corey, E. J., Beames, D J. *J. Amer. Chem. Soc.* 1972, 94, 7210 and Seebach, D., Neumann, H *Chem. Ber.* 1974, 107, 847.

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