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FUNCTIONALIZED ARYLLITHIUM INTERMEDIATES.
A SYNTHESIS OF BENZOCYCLOBUTENES.

Peter D. Brewer, Jayaram Tagat, Charles A. Hergrueter and Paul Helquist
Department of Chemistry, State University of New York at Stony Brook,
Stony Brook, New York 11794 USA

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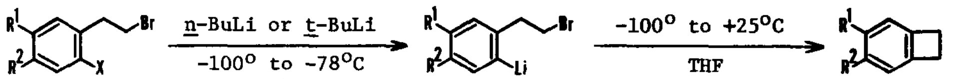
Benzocyclobutenes[1] have been found to be quite useful species for the synthesis of several types of compounds, including members of the alkaloid,[2] steroid,[3] and polycyclic terpenoid[4] classes of natural products. The key step in each of these syntheses may be rationalized in terms of a (2+4) cycloaddition of an unsaturated compound to the quinodimethane resulting from ring-opening of the benzocyclobutene.[5] In consideration of the many uses of benzocyclobutenes, the need for efficient, convenient methods for preparing these compounds is readily apparent.[6]

In connection with work directed toward the synthesis of other ring systems, we had occasion to investigate the conversion of several 2-(2'-halophenyl)ethyl bromides (1a-d)[7] to the corresponding aryllithiums (2a-d), which react with various added electrophilic species.[8] However, because of the importance of benzocyclobutenes and because of a recent contradictory statement (vide infra), we wish to report that in the absence of added reactants the aryllithiums (2a-d)readily undergo very efficient cyclization to afford the benzocyclobutenes (3a-d)[9] in isolated, overall yields of 87, 93, 91 and 96%, respectively (equation 1).[10]



1 2 3 (1)

a, R^1=R^2=H, X=Br
b, R^1=OCH_3, R^2=H, X=I
c, R^1=R^2=OCH_3, X=I
d, R^1,R^2=OCH_2O, X=I

Earlier, Parham and co-workers had reported a sole, simple example of this reaction sequence to give the parent benzocyclobutene (3a) in a yield of 68%[6d]. However, other authors, in the course of discussing the advantages of their own, more recent method for benzocyclobutenes, indicated that Parham's approach would not readily lend itself "to the preparation of benzocyclobutenes with an oxygenated aryl ring".[2] Quite to the contrary, our work has demonstrated that the lithium-halogen exchange reactions of 2-(2'-halophenyl)ethyl bromides and subsequent cyclizations provide a very efficient route to these very useful compounds. A typical procedure follows.

4-Methoxybenzocyclobutene (3b). To a solution of 1b (0.100g,0.293 mmol) in ether (2ml) at -78° under nitrogen was added a 2.40*M* solution (0.146 ml, 0.350mmol) of *n*-butyllithium in hexane over a 5-min period. After 1 h, THF (2 ml) was added, and the mixture was allowed to warm slowly to 25° and then washed with water. Isolated from the organic phase was 0.0366g (93%) of pure 3b as a clear, colorless oil: ^{1}H-nmr ($CDCl_3$) δ 6.52-7.18 (m, 3H, Ar-*H*), 3.73 (s, 3H, $-OCH_3$), and 3.07 (s, 4H, $-CH_2CH_2-$).

We are currently exploring cycloaddition reactions of the alkoxy-substituted benzocyclobutenes and further uses of the aryllithiums (2a-d) leading to naturally occurring compounds.

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FOOTNOTES AND REFERENCES

1. For a review of benzocyclobutene chemistry see I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970).
2. For a new synthesis of benzocyclobutenes and several leading references to the uses of these compounds in alkaloid synthesis see R. J. Spangler and B. G. Beckmann, *Tetrahedron Lett.*, 2517 (1976).
3. T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, H. Matsumoto, and K. Fukumoto, *J. Am. Chem. Soc.*, **99**, 3461 (1977).
4. T. Kametani, Y. Hirai, F. Satoh, and K. Fukumoto, *J. Chem. Soc., Chem. Commun.*, 16 (1977).
5. T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *Tetrahedron*, **31**, 949 (1975).
6. For some recent methods see a) R. L. Hillard and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **99**, 4058 (1977); b) R. P. Thummel and W. Nutakul, *J. Org. Chem.*, **42**, 300 (1977); c) R. Victor, *Transition Metal Chem.*, **2**, 2 (1977); d) W. E. Parham, L. D. Jones and Y. A. Sayed, *J. Org. Chem.*, **41**, 1184 (1976); e) P. G. Sammes, *Tetrahedron*, **32**, 405 (1976); f) H. Straub, *Tetrahedron Lett.*, 3513 (1976); g)E. Cuthbertson, and D.D MacNicol, *ibid.*, 1893 (1975).
7. Compounds 1a-d are conveniently available by routes discussed in detail elsewhere.[6d,8]
8. C. A. Hergrueter, P. D. Brewer, J. Tagat, and P. Helquist, submitted for publication.
9. All of these benzocyclobutenes, which are previously known compounds,[2,6a,b,d,g] were identified by comparison of spectra with published data.
10. THF is added to the reaction mixtures to effect more rapid cyclization. Alternatively, 3a-d may be obtained directly by performing the exchange reaction in THF.