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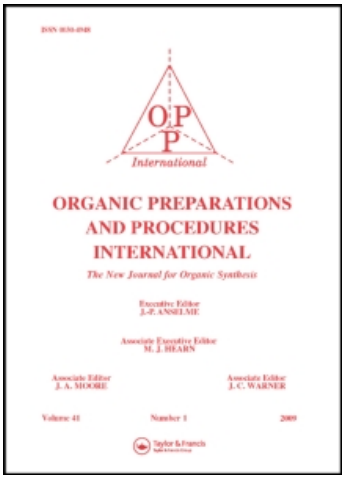

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AN EFFICIENT SYNTHESIS OF 4,5-DIMETHOXYBENZOCYCLOBUTENE via THE PARHAM CYCLIALKYLATION REACTION†

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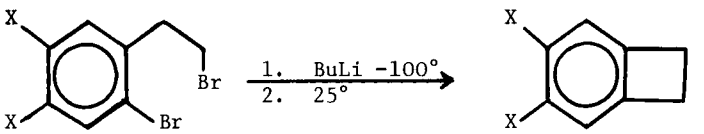
Parham and his students devised a general synthesis of benzocycloalkenes which afforded benzocyclobutene IIa in 68% yield from o-bromophenethylbromide (Ia).[1] In view of the importance of benzocyclobutenes as



I a) X = H b) X = OCH_3 II

diene precursors in 1,4-cycloaddition reactions,[2] we undertook to apply the Parham cyclialkylation to the synthesis of some oxygenated derivatives of benzocyclobutene. While multi-step routes to the 4-methoxy-[3-5] and 4,5-dimethoxy-[5] derivatives had been reported before our work began, the overall yields claimed were quite low. A newer, more direct pyrolytic method[6] which has been used to prepare milligram quantities of several oxygenated benzocyclobutenes has the disadvantage of requiring specially constructed apparatus. After completion of our synthesis of the 4,5-dimethoxybenzocyclobutene (IIb) a communication by Helquist, et al.[7] revealed that they also have extended the Parham cyclialkylation reaction to the preparation of IIb as well as to two other oxygenated analogs. Helquist provided incomplete information concerning the preparation of intermediates, but it is clear that the halide which they used in the

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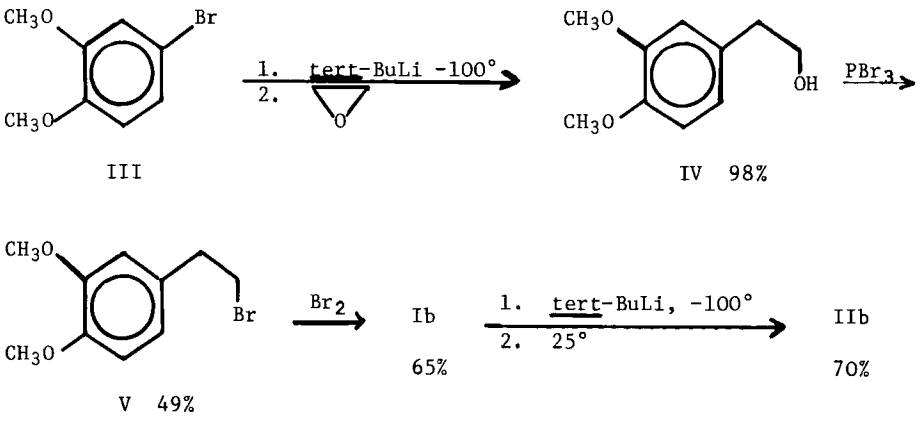
final cyclization to yield IIb was different from our own. In view of the continuing need for 4,5-dimethoxycyclobutene as a synthetic intermediate, it seemed desirable to publish our useful directions on how it may be prepared from 4-bromoveratrole in four steps and in an overall yield of 22%.

The first intermediate, 3,4-dimethoxyphenethyl alcohol (IV),[8,9] was prepared in 98% yield from 4-bromoveratrole (III) via halogen-metal exchange with t-butyllithium[9] at -100° followed by treatment with ethylene oxide. Conversion of the phenethyl alcohol (IV) to the corresponding phenethyl bromide (V) was carried out essentially as described by Sugasawa[10] and the bromide (V) was brominated in 65% yield to afford



2-bromo-4,5-dimethoxyphenethyl bromide (Ib). Selective halogen-metal exchange of the aryl halogen atom of the dibromo compound Ib occurred readily, and in contrast to the parent compound (Ia), cyclization of the organolithium intermediate to the cyclobutene derivative appeared to occur immediately at -100° (70% yield). The greater tendency of the oxygenated lithio derivative to undergo cyclization could be attributed to a para methoxy resonance effect leading to enhanced electron density at the 2 position.

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EXPERIMENTAL

3,4-Dimethoxyphenethyl Alcohol (IV). - A solution of 4-bromoveratrole (13.63 g, 0.063 mol) in a mixture of 120 ml of dry tetrahydrofuran and 30 ml of dry hexane in a 500 ml three-neck flask provided with a mechanical stirrer and having a static dry nitrogen atmosphere was cooled to -100° and through a pressure equalizing funnel a pentane solution of t-butyllithium (70.0 ml of 1.8 M solution, 0.126 mol)[11] was added at such a rate that the temperature did not exceed -95°. After an additional 5 min at -100°, ethylene oxide (5.28 g, 0.120 mol) in 40 ml of dry tetrahydrofuran was added dropwise. Stirring was continued for an additional 30 minutes at -100° after which the mixture was allowed to warm to room temperature. The mixture was poured into 300 ml of water, the organic layer separated and the aqueous layer repeatedly extracted with ether (5x100 ml). The combined organic solutions were dried and concentrated (rotary evaporator). The residual oil, 11.28 g (98% yield) solidified, mp 37-38°, lit.[12] mp. 36°, and required no further purification: IR (neat) 3400 cm^{-1}; ^1H NMR[12] ($CDCl_3$) δ 2.45 (bs, 1, OH), 2.81 (t, 2, CH_2), 3.78 (t, obscured, 2, CH_2), 3.83 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 6.62 - 6.90 (m, 3, ArH).

3,4-Dimethoxyphenethyl Bromide (V). - The conversion of IV to the bromide was accomplished at 0-25°[13] essentially as described by Sugasawa[10] (49% yield); ^1H NMR ($CDCl_3$) δ 3.08 (t, 2, CH_2), 3.52 (t, 2, CH_2), 3.85 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 6.70 - 6.98 (m, 3, ArH).

2-Bromo-4,5-dimethoxyphenethyl Bromide (Ib). - To a solution of 6.32 g (0.026 mol) of the bromide V in 100 ml of acetic acid a solution of 6.08 g (0.038 mol) of bromine in 80 ml of acetic acid was added dropwise with stirring. After an additional 30 minutes the mixture was poured into water which was extracted with chloroform (5x100 ml). The extract

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was dried and concentrated and the residue distilled under reduced pressure affording 5.8 g (69%) of the dibromo compound Ib, bp. 98-99° (0.02 torr). This material was pure enough for analysis and further reactions and on standing, crystallized, mp. 54-55°. A small sample was recrystallized from ethanol to constant mp. 59-60°. IR (neat) 3010, 2970, 2940, 2850, 1600, 1520, 1500, 1460, 1440, 1385, 1320, 1270, 1210, 1160, 1115, 1030, 955, 855, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.19 (t, 2, CH_2), 3.57 (t, 2, CH_2), 3.83 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 6.68 (s, 1, ArH), 6.92 (s, 1, ArH).

Anal. Calcd for $C_{10}H_{12}Br_2O_2$: C, 37.06; H, 3.73; Br, 49.33.
Found: C, 36.89; H, 3.88; Br, 49.11.

4,5-Dimethoxybenzocyclobutene (IIb). - A mixture of 125 ml of tetrahydrofuran, 30 ml of hexane and 4 g (0.012 mol) of the dibromide 3 was placed in a 250 ml three-neck flask equipped as in the preparation of IV and cooled to -100°. t-Butyllithium (13.3 ml of a 1.8 M solution in pentane, 0.024 mol)[11] was added at such a rate that the temperature did not exceed -95°. The reaction mixture was then stirred for one hour at -100° and then allowed to warm to room temperature. The mixture was next poured into 250 ml of water, the organic layer separated and the aqueous phase extracted with ether (3x100 ml). The combined organic solutions were dried and concentrated under reduced pressure. The solid residue 1.79 g (91%), mp. 89-92° was recrystallized from hexane to afford 1.37 g (70%) of pure 4,5-dimethoxybenzocyclobutene as colorless needles, mp. 96-98°, lit.[14] 98.5-100°; ^1H NMR[16] ($CDCl_3$) δ 3.14 (s, 4, CH_2), 3.89 (s, 6, OCH_3), 6.63 (s, 2, ArH).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37.
Found: C, 73.27; H, 7.23.

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REFERENCES

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1. W. E. Parham, L. D. Jones and Y. A. Sayed, J. Org. Chem., 41, 1184 (1976).
2. I. L. Klundt, Chem. Rev., 70, 471 (1970).
3. T. Kametani and K. Fukumato, Heterocycles, 3, 29 (1975).
4. T. Fleming, F. L. Gianni and T. Maki, Tetrahedron Lett., 881 (1968).
5. T. Kametani, M. Kajiwara, T. Takahashi and K. Fukumoto, Tetrahedron, 31, 949 (1975).
6. R. J. Spangler, B. G. Beckmann and J. H. Kim, J. Org. Chem., 42, 2898 (1977).
7. P. D. Brewer, J. Tagat, C. A. Hergrueter and P. Helquist, Tetrahedron Lett., 4373 (1977).
8. J. D. Fulton and R. Robinson, J. Chem. Soc., 1463 (1933).
9. The reaction of 3,4-dimethoxyphenyllithium with ethylene oxide is not new. An earlier effort used n-butyllithium in the metal-halogen exchange and the yield of IV was about 31%; M. Lora-Tomayo, R. Madronero and G. G. Munoz, Chem. Ber., 93, 289 (1960).
10. S. Sugasawa, J. Pharm. Soc. (Japan), 57, 296 (1937).
11. D. Seebach and H. Neumann, Chem. Ber., 107, 847 (1974) have shown that in the absence of a second equivalent of t-butyllithium significant loss of the aryllithium occurs through dehydrohalogenation of the t-butyl bromide formed in the exchange.
12. S. Takano, K. Ogasawara, I. Nagayama and T. Kutsuma, Synth. Comm. 6, 349 (1976).

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13. Cf., E. Campaigne and B. G. Heaton, J. Org. Chem. 29, 2372 (1964).

14. T. Kametani, M. Kajiwara, T. Takahashi and K. Fukumoto, Tetrahedron, 31, 949 (1975).

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