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MASKED ARENES; SYNTHESIS OF SUBSTITUTED BENZENES AND BENZENE OXIDES

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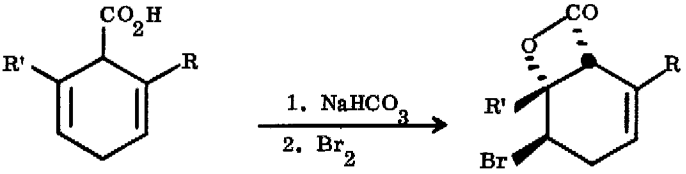
The fragmentation of simple four-membered lactones to carbon-carbon double bonds is a classic reaction in organic chemistry, although uncommonly used in synthesis.[1, 2] Herein we describe how β-lactones can serve as disguised alkenes in constructing functionalized aromatics and arene oxides under mild conditions from alicyclic precursors.

Early in the course of our own studies on the halogenation of dihydrobenzoic acids, Barnett reported[3,4] that the bromination of such compounds in the form of their sodium salts represents a general source of halo-β-lactones (equation 1).

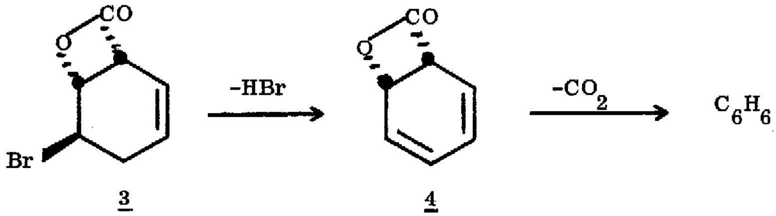
(1)



1 R, R' = H

2 R = H, R' = alkyl

This outcome led us to consider whether a non-nucleophilic base might effect the dehydrobromination of 3 thereby producing 4. This diene, formally the 2+2 cycloadduct of benzene and carbon dioxide, would be expected to aromatize rapidly with extrusion of CO_2.

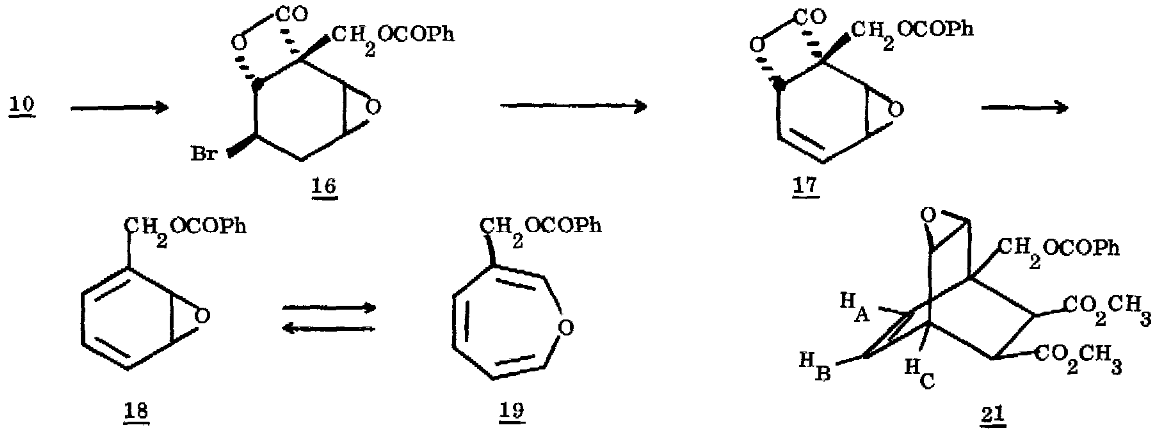


In fact stirring a solution of the parent β-lactone with one equivalent of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in CHCl$_3$ at -10° furnishes benzene in quantitative yield. We have, however, been unable to observe the presumed intermediate lactone 4 by low temperature nmr spectroscopy. Since its fission might be acid-catalyzed (e.g. by DBU•HBr) we have also experimented with lithium dialkylamides as the agents for HBr elimination. In such reactions benzoic acid becomes the major product, and although it too may be derived from 4 by an elimination-rearrangement, no spectroscopic evidence supporting the temporary existence of 4 has been obtained to date.

This reconstruction of aromatic rings has proven to be general. The alkylation of 1 and 2 as their dianions provides a practical synthesis of 1-substituted-1,4-dihydrobenzoic acids,[5] all of which seem to undergo bromo-β-lactonization in good yield. This fact makes it a simple matter to prepare a variety of *ortho*-substituted benzenes from nonaromatic rings as shown in Table 1.[6]

Usually DBU is the most effective reagent for dehydrobromination of the halolactones, however attempted aromatization of 8 by this technique affords only a low yield of benzyl alcohol. The co-occurrence of partially characterized high molecular weight products containing DBU residues suggests that N-acylation of this "non-nucleophilic" base competes with β-lactone fragmentation.[3] Essentially the same result prevails using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), a base which has recently been reported to undergo nucleophilic additions.[7] All such problems were readily circumvented by using freshly distilled triethylamine in place of DBU.

The gentle nature of this diene unmasking process is especially well-suited to the synthesis of biologically important arene oxides. For example, lactone benzoate 10 undergoes stereospecific peracid-mediated epoxidation in 90% yield. Dehydrobromination of 16[8] (4 hr, 0° → rt, DBU) affords the acid-sensitive epoxyalkenyllactone 17 (91%) which is isolated but not purified. Upon heating at 70°, 17 smoothly loses CO$_2$ to form dienoxide 18 (>90%).[8] This arene epoxide, in equilibrium with its oxepin valence tautomer 19, can be trapped efficiently with maleic anhydride. The Diels-Alder adduct 20 [mass spectrum (CI, CH_4) 327 (M+1), 355 (M+29)] was characterized as its dimethylester 21, obtained pure after hydrolysis of 20 (Na_2CO_3), diazomethane treatment and silica gel chromatography; [mp 107-109°; IR (λ_{max} $CHCl_3$) 5.75 - 5.82 (broad), 6.22μ; NMR (δ, $CDCl_3$) 8.05, 7.45 (2 multiplets, 5H, benzoate), 6.12, 5.82 (ABX, 2H, $J_{AB}=9$, $J_{BC}=6$), 4.60 (broad s, 2H, merged AB quartet), 3.59 (s, 3H), 3.54 (s, 3H), 3.42 - 3.15 (complex m, 5H)].[8]



We have also observed (see Table 1) that merely heating the olefinic bromo-β lactones in a Kugelrohr apparatus (130°, 3 hr) results in a 1,2-Br migration concomitant with expansion of the lactone to its thermodynamically more stable γ-isomer (equation 2). Such a stereospecific rearrangement is known to occur in monocyclic iodo-β-lactones[9] and represents a useful access to derivatized bicyclic γ-lactones.

(2)

These general transformations indicate the considerable utility of four-membered lactones in preparative organic chemistry. Further details of our new arene oxide methodology as it pertains to the synthesis of complex natural products will be reported in due course.

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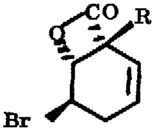
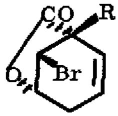
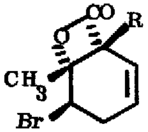
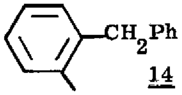
TABLE 1

"Synthesis of Aromatics from Bromo-β-Lactones Using DBU"

β-lactone (% yield)	mp[a]	arene (% yield)[b]	γ-lactone (% yield)[c]
 3 R=H (40)	84-5°	benzene (quant.)[d]	 5 (5-10)
6 R=CH_3 (78)	76-79°	toluene (quant.)[d]	7 R=CH_3 (70) mp 76.5-77.5°
8 R=CH_2OH (86)	--	benzyl alcohol (70)[e]	9 R=CH_2OH (81)
10 R=CH_2OCOPh (ppd. from 8, (>95))	119-22°	benzyl benzoate (96)	11 R=CH_2OCOPh (70)
 12 R=H (30)	52-53°	toluene (quant.)[d]	--------
13 R=CH_2Ph (45)	--	 (92) 14	--[f]
15 R=CH_3 (62)		o-xylene (>95)[d]	---------

(a) Satisfactory elemental analyses have been obtained for all new β-lactones. (b) To a solution of each bromo-β-lactone in $CHCl_3$ was added DBU (1.2 equiv) at 0°. After warming to rt over 30 min, each product was isolated by extraction and identified by comparison with an authentic sample. (c) These compounds exhibited ir and nmr absorptions consistent with their assigned structures. (d) This experiment was performed in an nmr tube. (e) Et_3N (2 equiv) was substituted for DBU. (f) This β-lactone afforded only 14 when heated.

References and Footnotes

(1) For reviews of β-lactone chemistry see (a) H. A. Zaugg, Organic Reactions, 8, 306 (1954); (b) K. Kroper, Methoden der Organischen Chemie (Houben-Weyl) 6/2, 515 (1963)

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(7) D. C. Palmer, M. J. Strauss, Tetrahedron Lett., 1431 (1976)

(8) Satisfactory elemental analysis has been obtained for this compound.

(9) W. E. Barnett, W. H. Sohn, J. Chem. Soc. Chem. Commun., 472 (1972)