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THE BIRCH REDUCTION/ALKYLATION OF PHTHALIDES

THE SYNTHESIS OF SOME SUBSTITUTED BICYCLO[3.2.1]OCTANES

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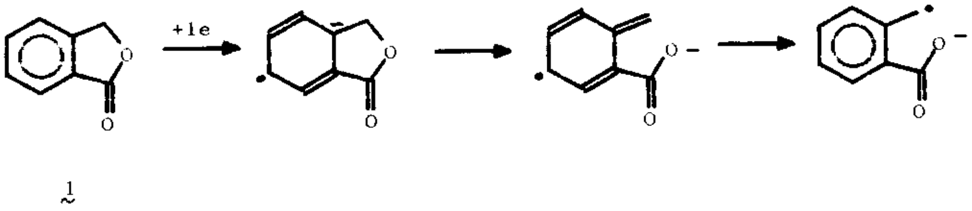
Abstract - The first successful reductions of the aromatic rings of phthalides, with the preservation of the lactone rings, are reported. The reduction/alkylation of some substituted 4-methoxyphthalides gave lactonic enol ethers, which were converted into conjugated homocyclic dienes and further into cyclohexenones. These enones were easily converted into bicyclo[3.2.1]octanes by the Bu_3SnH/AIBN free radical cyclization reaction.

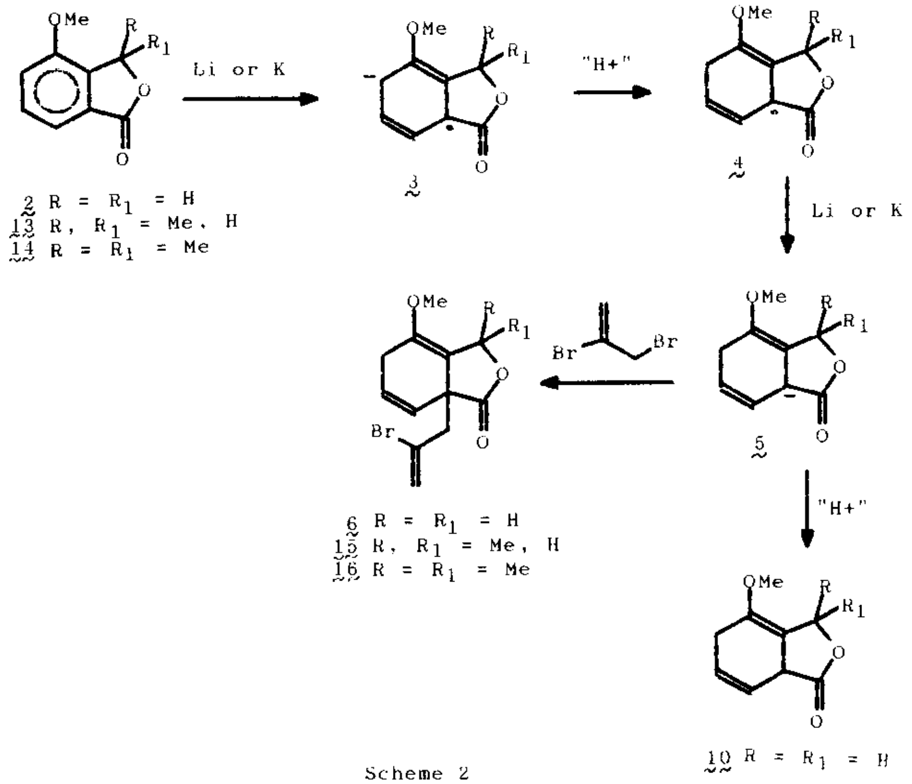
INTRODUCTION

The Birch reduction reaction is routinely used for converting benzenoid aromatic molecules into useful alicyclic synthons (ref. 1). Nevertheless, the transformation of phthalides (1) by this process has not been reported. One possible outcome of the Birch reduction of a phthalide would be the cleavage of the lactone ring to produce a 2-methylbenzoate (Scheme 1).

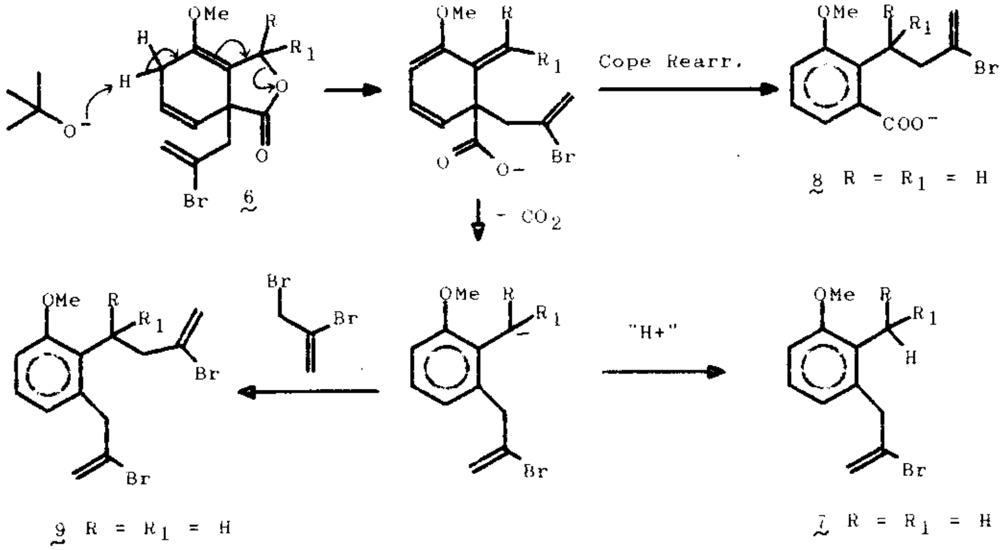


Scheme 1

However, the optimal molecular geometry for this cleavage, and for π-σ* overlap, has the C-3-O-2 bond orthogonal to the aromatic ring. Since the phthalide (1) is completely coplanar, a lactone cleavage cannot be the primary result of the Birch



Scheme 2



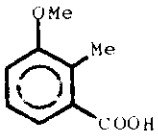
Scheme 3

reduction process. This analysis suggested that the reduction of the phthalide (2), Scheme 2, and trapping the carbanion (5) with 1,2-dibromopropene should yield an intermediate which was suitable for conversion into a bicyclo[3.2.1]octane by a free radical cyclization reaction.

DISCUSSION

The Birch reductions and alkylations of 4-methoxyphthalide (2) were performed in tetrahydrofuran (THF)/ammonia solvent mixtures, using the standard reaction conditions (ref. 1). In a typical reaction, very small pieces of potassium were added slowly to a rapidly stirred solution of the phthalide in a 2:1 mixture of liquid ammonia and THF, at -78 °C, containing 1.1 equivalents of a proton donor, until the blue colour of excess electrons was observed. Usually, about 2.1 equivalents of potassium were used and the excess of electrons was destroyed by the careful addition of small quantities of 1,2-dibromoethane. The reaction mixture was then allowed to warm to about -20 °C, under a stream of dry nitrogen, and was kept at this temperature until no more ammonia was released (ref. 2). The reaction mixture was then cooled back to -78 °C and the carbanion was quenched with 1.1 equivalents of 1,2-dibromopropene. After stirring for 25 minutes, the reaction mixture was diluted with aqueous ammonium chloride and was worked up.

When tertiary butanol (t-BuOH) was used as the proton donor, the compounds (2), (6), (7), (8) and (9), were isolated in 42%, 15%, 10%, 13% and 20% yields respectively. Further, if (after addition of the metal) the reaction mixture was quenched with a large amount of ammonium chloride, then the acid (11) was the major product (50%) and none of the desired lactone (10) was found.



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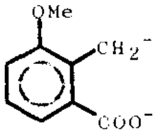

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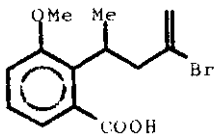
Since the planar intermediate (5) cannot be converted directly into the carbanion (12), then the compound (8) could not have been produced by a simple transformation of anion (5). Instead, it seemed more likely that the lactone (6) had been produced but was further transformed by t-butoxide, generated from the t-BuOH. Indeed, when ammonium acetate was used as the proton donor in the reaction of the compound (2), the compound (6) was obtained in 91% yield and none of the compounds (7), (8) or (9) were produced.

The reduction/alkylation of the phthalides (13) and (14) using t-BuOH and potassium gave modest yields (about 50%) of the lactones (15) and (16) respectively. The compound (17) was also isolated (in 10% yield) from the reaction of phthalide (13), but no analogous material was found in the reaction of phthalide (14). However, by using ammonium acetate and either lithium or potassium, the lactones (15) and (16) were produced in 94% and 95% yield respectively. These results confirmed the adverse role played by the t-butoxide and the production of the compounds (7), (8) and (9) could now be rationalized as in Scheme 3.



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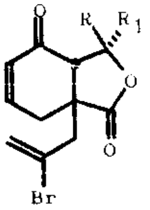
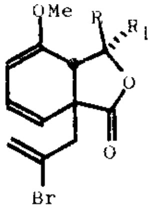


18 $R = R_1 = H$
19 $R, R_1 = Me, H$
20 $R = R_1 = Me$



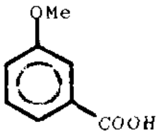
21 $R = R_1 = H$
22 $R, R_1 = Me, H$
23 $R = R_1 = Me$

The compounds (6), (15) and (16) were quantitatively converted into the unsaturated ketones (18), (19) and (20), by acidic hydrolyses, without cleavage of the lactone rings. The compounds (6), (15) and (16) were also quantitatively isomerized to the conjugated dienes (21), (22) and (23), after being stored at -5 °C (in the pure state) for several days.

Normally, β-alkoxy-, or β-acyloxy-enol ethers undergo elimination of the β-leaving group during acidic hydrolyses, to give unsaturated ketones (ref. 3). Further, the reduction and alkylation of m-anisic acid (24) gave enol ethers (25), which were structurally similar to the lactones (6), (15) and (16), but which did not spontaneously undergo conjugation (ref. 4). These data suggest that during the acidic hydrolyses of the lactones (6), (15) and (16), they were first isomerized into the conjugated dienes, which then were hydrolysed to the observed unsaturated ketones. Once again the planar geometry of the lactones (6), (15) and (16) provided the stereo-control necessary for the successful production of the desired materials from the phthalides.

The diastereoisomeric lactones (15) were inseparable, but were detectable and quantifiable by nmr which showed that there was a marked selectivity in the formation of one diastereoisomer. The unsaturated ketones (19-exo) and (19-endo) were easily separated by column chromatography and these compounds enabled the complete characterization of the lactones (15) by nuclear Overhauser effect studies (at 400 MHz). Exo- and endo- refer to the molecular surface on which the methyl group lies. When the reduction of phthalide (13) was done under the standard conditions (ref. 1), without removing the ammonia, the isomers (15-exo) and (15-endo) were obtained in a 1:1 ratio. However, by removing the ammonia before alkylation, the isomers were obtained in a 1:10 ratio (exo- to endo-).

The analogous Birch reductions (ref. 4) of ammonium 4-methylbenzoate (from the solution of 4-methylbenzoic acid in ammonia/THF) also yielded an unequal mixture of stereoisomers (26), demonstrating that this diastereoselectivity was solvent regulated rather than being due to any special feature of the phthalide, or benzoate. These solvent dependent facial selectivities might be consequences of aggregation phenomena (ref. 5) and could be developed into a valuable strategy for manipulating these reductions.



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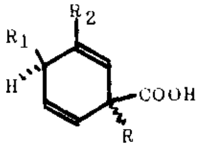
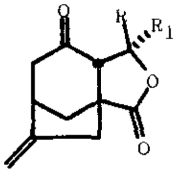


25 R_1 = H, R_2 = OMe
26 R_1 = Me, R_2 = H



27 R = R_1 = H
28 R, R_1 = Me, H
29 R = R_1 = Me

The desired bicyclo[3.2.1]octanones (27), (28) and (29) were prepared by the very slow addition of tributyltin hydride and azobisisobutyronitrile (AIBN) to dilute solutions of the unsaturated ketones (18), (19) and (20) respectively, in refluxing benzene (ref. 6), over a period of two hours. The reactions were usually refluxed for an additional hour following the addition of the reagents. These radical cyclizations proceeded nearly quantitatively.

These bicyclo[3.2.1]octanones possess some of the features of the rings C and D, as well as "handles" for the construction of the rings A and B, of the kauranoid and derived diterpenes. The efficiency of this synthesis and the possibility of using more highly substituted phthalides to produce more complex bicyclo[3.2.1]octanes demonstrates the synthetic potential of this route.

All new compounds gave satisfactory analytical and spectroscopic data, which were completely consistent with the suggested structures.

ACKNOWLEDGMENTS

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