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REACTION OF DI(BROMOMAGNESIO)ALKANES WITH UNSYMMETRICALLY SUBSTITUTED CYCLIC ANHYDRIDES

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Abstract Alkylated γ-spirolactones were prepared in one-step reactions in high yields from butane-1,4-diyl and pentane-1,5 diyldimagnesium dibromides and substituted cyclic anhydrides in tetrahydrofuran In the light of experimental findings electronic and steric factors influence the regiospecificity of this reaction

A variety of methods has been reported for the synthesis of substituted spirolactones[1-8] However, this methodology normally requires the use of complex reagents and several steps to synthesize the butanolide system

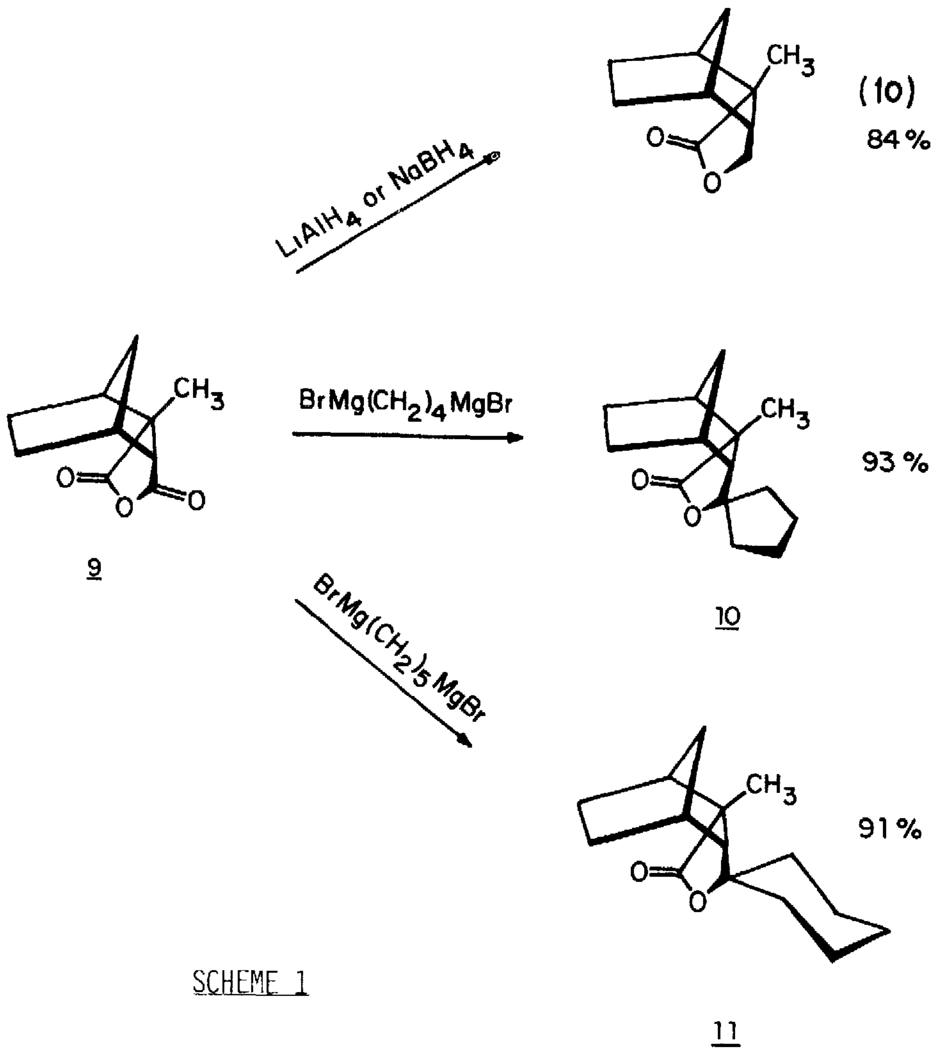
Recently, we have found that symmetrical cyclic anhydrides are converted in good yield to the corresponding spirolactones[6] As a consequence of the general importance of alkylated lactones, it became important to examine the extension of this annelative method to the synthesis of 2-substituted-4-spiro-γ-lactones The proposed methodology involves the addition of di(bromomagnesio)alkanes to the unsymmetrically substituted cyclic anhydrides The Grignard di-reagents are readily prepared and react with a variety of substituted anhydrides This cyclization provides a novel, versatile and regioselective route for synthesizing γ-lactones

Another interesting aspect of this work is the study of regioselectivity as compared to the reduction of similar compounds with metal hydrides In contrast to the plethora of information available on reductions, an examination of the literature reveals that systematic studies of Grignard additions to cyclic anhydrides are lacking[8-11]

It has been demonstrated that the regioselectivity of metal hydride reduction takes place principally at the carbonyl group adjacent to the more highly substituted carbon atom The only exceptions reported are exo-2-methylbicyclo[2 2 2]oct-5-ene-endo-2,3-dicarboxylic anhydride and exo-2-methylbicyclo[2,2,1]hept-5-ene-endo-2,3 dicarboxylic anhydride[10], which lead, by stereospecific addition, to an unique crystalline lactone at the less highly substituted carbonyl group

In the course of our work on reactions of Grignard di-reagents with cyclic anhydrides, we observed that regioselective nucleophilic addition is oriented to the less hindered carbonyl group for all anhydrides studied

The steric bulk of methyl, dimethyl or phenyl groups appears to affect the course of the reaction for both di(bromomagnesio)alkanes In contrast to the hydride reduction reaction, preferential attack takes place at the more accessible carbonyl group, followed by a second nucleophilic addition to the intermediate ketone leading to five or six carbon annelation At this stage, we observed an appreciable difference in the respective yields when using 1,4-di(bromomagnesio) butane as compared to 1,5-di(bromomagnesio)pentane, particularly when this reaction is performed with monocyclic and aromatic cyclic anhydrides. Furthermore, the regioselectivity is higher for the reactions leading to cyclohexanes rather than to cyclopentanes



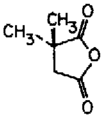
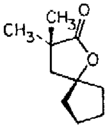
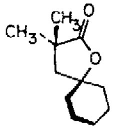
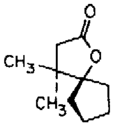
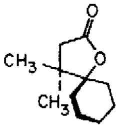
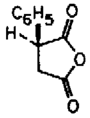
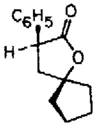
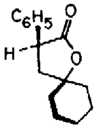
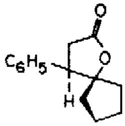
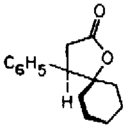
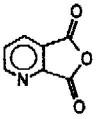
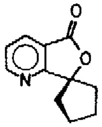
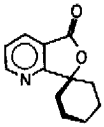
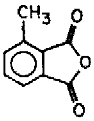
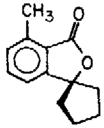
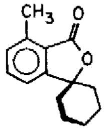
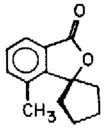
SCHEME 1

In both cases the results are the contrary of those of metal hydrides[10] except for the exo-2-methylbicyclo[2 2 1]hept-4-ene-endo-2,3 dicarboxylic anhydride which leads by stereospecific addition to unique spirolactones[12]

In an attempt to expand the scope of this method we used the heterocyclic dicarboxylic anhydride (3), but under the same reaction conditions the complex was insoluble and the yield of lactone was lower for both di(bromomagnesio)alkanes The starting 2,3-pyridine dicarboxylic acid or anhydride was not recovered and the reaction gave polymeric by-products Only a single isomeric spirolactone was produced in this case This regiospecificity may be attributed to the presence of the nitrogen atom.

The standard preparation of the Grignard di-reagent is as previously described[13]. The temperature of addition is not critical, but since the reaction is exothermic it is usually effected in the cold This reaction was performed by treatment of the anhydride with an

TABLE 1

Starting Anhydride	Products with $BrMg(CH_2)_4MgBr$	Yield %	a b ratio	Products with $BrMg(CH_2)_5MgBr$	Yield %	a b ratio
 1	 1a	1a 80	3 2	 5a	70	4 1
	 1b			 5b		
 2	 2a	73	3 1	 6a	55	3 1
	 2b			 6b		
 3	 3b	55		 7b	20	
 4	 4a	75	5/2	 8a	60	
	 4b					

equimolar amount of di(bromomagnesio)alkane After hydrolysis with 10% HCl and work-up in the usual manner the mixtures of two regioisomeric spirolactones were separated by column chromatography[14] (Table 1)

In summary, it would appear that this method allows for the spiroannelation of substituted anhydrides in a specific manner The generalization of these findings and their applications to the synthesis of natural compounds are the objective of a future investigation

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14 All yields reported in Table 1 refer to chromatographically isolated pure material

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