

A FACILE AND GENERAL ROUTE TO 4-SUBSTITUTED-2 BUTENOLIDES

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Summary - Grignard reagents react with 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride and produce in high yields the corresponding substituted bicyclo- γ -butanolides. These lactones produce the title compounds by retro Diels-Alder reaction during distillation.

Previously, we have demonstrated that the action of di(bromomagnesio)alkanes with dicarboxylic cyclic anhydrides gave the corresponding spiro lactones.^{1,2} In a one-step reaction, this methodology was found to be general to most anhydrides with the exception of maleic anhydride which gave a mixture of several compounds.³

We describe herein a new and important aspect of this methodology which permits the synthesis of a series of bicyclobutanolides. These compounds have not been described previously and their preparation is difficult by published methods. Another important aspect of this work is the synthetic value of the bicyclo- γ -butanolides as precursors of 4-substituted-2-butenolides obtained by retro Diels-Alder reactions. Finally, we generalize the reaction of Grignard reagents (RMgX) with cyclic anhydrides in order to demonstrate that this method is an easy route for synthesizing the corresponding lactones. In the course of our investigation of reactions of di- and mono-Grignard reagents with cyclic and bicyclic anhydrides, we have observed that the 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride reacts particularly readily with a variety of Grignard reagents to give three different types of lactones: 1) 4,4-dialkylbicyclobutenolides obtained with a primary organomagnesium compounds; 2) 4-alkylbicyclobutenolides with secondary organomagnesium compounds via a reduction process and 3) spiro 4-bicyclobutenolides with di-primary dimagnesium compounds. (Tables I, II and III).

The Grignard reagent (RMgX) is best prepared in diethyl ether solution. The 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride is only slightly soluble in this solvent; but it is soluble in THF or in benzene. In the case of primary alkylmagnesium halides either THF or benzene can be used whereas in THF solution di-Grignard reagents (BrMg(CH₂)_nMgBr) give the spiroannulated products quantitatively without by-products. In the case of secondary magnesium bromides THF is preferred to benzene⁴ in order to suppress formation of 4,4-dialkyl- γ -lactone resulting from double addition of RMgX. The other by-product is the intermediate ketoacid which can be formed via the enolization process after hydrolysis. The separation of this ketoacid from the lactonic compounds is achieved by washing the reaction mixture with 10% NaOH solution. Lactonization is spontaneous upon acidification.

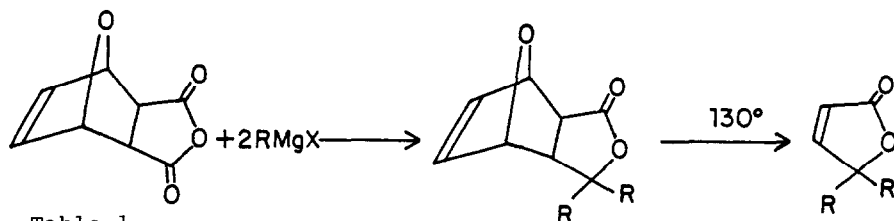


Table I

R		Mp/°C		Bp/mmHg	Mp/°C
n-C ₃ H ₇ -	1a	61		1b	128/7mm
n-C ₄ H ₉ -	2a	91		2b	146/7mm
n-C ₅ H ₁₁ -	3a	81		3b	124/.02mm
n-C ₆ H ₁₃ -	4a	80		4b	134/.02mm 35
C ₆ H ₅ -	5a	150		5b	160/.02mm 108
C ₆ H ₅ CH ₂ -	6a	164		6b	170/.02mm 132

As indicated in Table I, primary alkyl -and arylmagnesium halides give the corresponding 4,4-disubstituted bicyclo- γ -lactones (1a-6a) in high yield. These lactones are solid and were characterized on the basis of analytical and spectral data.⁵ The butenolides (1b-6b) were obtained after vacuum distillation of compounds (1a-6a) in quantitative yields.

The reactions of secondary alkylmagnesium halides with the same bicyclic anhydride produce the corresponding monoalkylbicyclobutanolides. The reduction process is summarized in Table II. Secondary Grignard reagents react with hindered ketones by this same reduction process.⁴ A similar study has not been previously reported for cyclic anhydrides and the results we report herein are interesting for synthetic and mechanistic purposes. The 4-alkylbutenolides are obtained as mixtures of the two possible diastereoisomers in the ratio 9:1. The isomers distribution results from the steric effect. It is apparent that the *endo* isomer is sterically preferred, so this reaction favors products with the alkyl groups in the *endo* position.⁵ After recrystallization only the *endo* compound is obtained, but as expected both isomers produce the same 4-alkylbutenolide 1d after heating under vacuum.

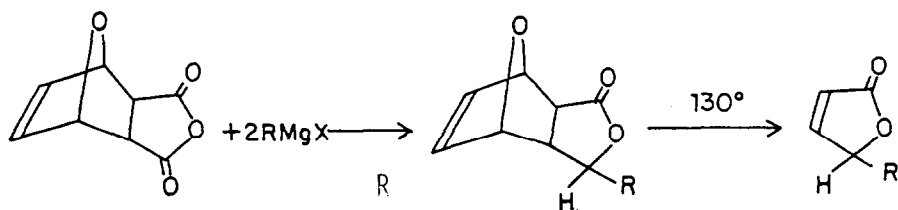


Table II

		Mp/°C		Bp/mmHg
$\begin{array}{l} \text{CH}_3 \\ \diagdown \\ \text{CH-} \\ \diagup \\ \text{CH}_3 \end{array}$	1c	79		1d 94/7mm
$\begin{array}{l} \text{CH}_3 \\ \diagdown \\ \text{CH-} \\ \diagup \\ \text{C}_2\text{H}_5 \end{array}$	2c	54		2d 106/7mm

Furthermore, analysis of reaction products indicates only 5% of 4,4-dialkyl- γ -lactone and 20% of ketoacid. These compounds correspond to the addition and enolization processes of the intermediate ketoacid. We extended this study to 2-butyilmagnesium bromide and found also that only the 4-monosubstituted bicyclo- γ -lactone (2b) is formed in good yield. It is clear that the corresponding 2-butenolide 2d is a mixture of the two diastereoisomers.⁶

The reaction of α,ω -di(bromomagnesio)alkanes with the same substrate such as the primary alkylmagnesium bromides gives the diaddition lactones with a small amount of by-products. The intramolecular addition to the intermediate ketoacid seems to be favored. The spirolactones are obtained in better yields (table II).

The bicyclo- γ -lactones are interesting intermediates for the preparation of 2-butenolides by retro Diels-Alder reaction. This method permits the facile synthesis of corresponding 2-butenolides from commercially available bicyclic anhydrides in a one-pot reaction, in contrast to the retro Diels-Alder methods previously described.⁷ Some of these 2-butenolides had been synthesized by considerably more complicated routes^{7,10}. The 2-butenolides prepared in the present work are mostly liquid except the 4,4-diphenyl and 4,4-dibenzyl-2-butenolides which are solids.^{5,11}

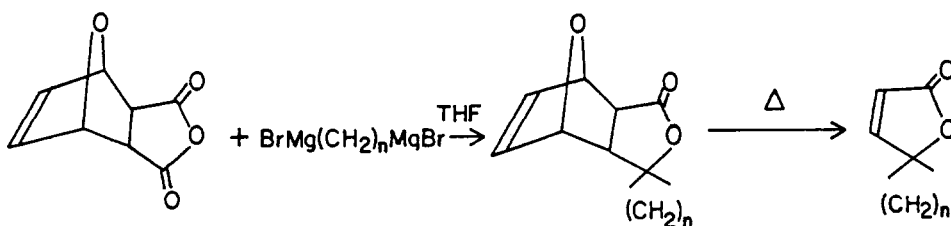


Table III

		Mp/ ^o C		Bp/mmHg
n=4	<u>1e</u>	81.5	<u>1f</u>	116/7
n=5	<u>2e</u>	94.5	<u>2f</u>	124/7

A typical experimental procedure is illustrated by the preparation of compound 1d. To the isopropylmagnesium bromide (0.96 mol) prepared in anhydrous ether (100 ml) under nitrogen is added dropwise at room temperature the 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride in anhydrous tetrahydrofuran (60 mL). The reaction mixture was stirred overnight under nitrogen. After hydrolysis with (HCl, 10%) at 0^oC and work-up in the usual manner, the lactone 1c was isolated by crystallization, m.p. 79-80^oC yield 77%. The butenolide 1d was obtained by vacuum distillation of 1c. B.P. 93-94/7mm Hg. Yield 95%. The diisopropylbicyclic lactone was separated by column chromatography through silica gel (high pressure), yield 8%, mp = 73^oC. The ketoacid compound was obtained as a viscous liquid by basic extraction. Yield 15%.

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References and notes

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2. P. Canonne, G. Lemay and D. Bélanger, *Tetrahedron Letters*, 4167 (1980).
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4. We reported previously that benzene increases the percentage of the alcohol arising from the addition reaction whereas THF favors the corresponding reduced alcohol. See P. Canonne, G. Foscolos and G. Lemay, *Tetrahedron Letters* 4383 (1979).
5. Satisfactory spectroscopic data (M.S. IR, ¹H-NMR) were obtained for all new compounds.
6. The ¹³C-NMR spectrum indicates the presence of the two diastereoisomers.
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11. Satisfactory elementary analyses were obtained for all the new compounds.

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