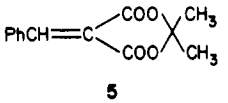
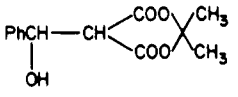
another very reactive electrophile. The following points



5



6

are noteworthy:

(1) The $K_1^{H_2O}$ values indicate that 1 is an even stronger (4.3-fold) Lewis acid than 5, but the *rate* constants for water and OH^- attack on 1 are lower than for attack on 5. This indicates a higher intrinsic barrier[5] toward nucleophilic addition in 1. A likely factor responsible for this difference in intrinsic barriers is that 2 derives its stability mainly from the delocalization of the negative charge into the carbonyl groups while this resonance factor is less important in the corresponding adduct of 5.[6] It is well established that intrinsic barriers in carbanion forming reactions increase with the degree of resonance stabilization of the carbanion.[8]

(2) $K_1^{H_2O}/K_a^{enol} = 0.50$ is the equilibrium constant for the conversion of 1 into 3 upon water addition. If one assumes that the extinction coefficient of 1 is the same in water and in acetonitrile one can calculate a $K_1^{H_2O}/K_a^{enol} = 0.69$ on the basis of the absorbance in aqueous 0.1 M HCl and in acetonitrile reported by Arnold et al.,[3a] in fair agreement with our value. There is no stable form derived from benzylidene Meldrum's acid which corresponds to 3; on the other hand formation of 6 is significant in the benzylidene Meldrum's acid, but no corresponding carbon protonated adduct is formed in the benzylidenemalonaldehyde system. This parallels the fact that the enol form of Meldrum's acid is very unstable[9] but that malonaldehyde exists virtually exclusively in the enol form.[10]

Acknowledgment. This work has been funded by Grant CHE-8315374 from the National Science Foundation.

Registry No. Benzylidenemalonaldehyde, 82700-43-4.

(5) Defined as $\Delta G^{\ddagger}$ when $\Delta G^{\circ} = 0$.

(6) A major factor responsible for the high proton acidity of Meldrum's acid and the high Lewis acidity of benzylidene Meldrum's acid is its bislactone structure.[7]

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(9) Eigen, M.; Ilgenfritz, G.; Kruse, W. *Chem. Ber.* **1965**, *98*, 1623.

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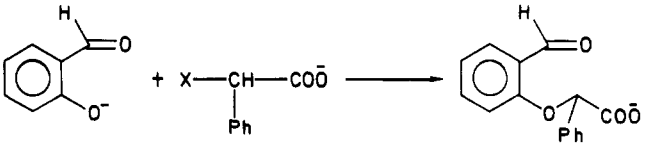
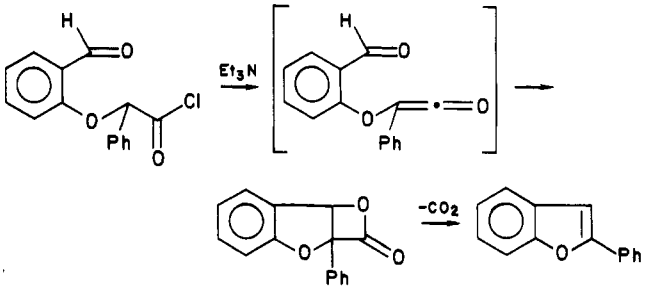
Intramolecular [2 + 2] Cycloaddition Reactions of Ketene and Carbonyl Groups. A New Synthesis of Benzofurans

Summary: (*o*-Carbonylphenoxy)acetyl chlorides are dehydrochlorinated to the corresponding (*o*-carbonylphenoxy)ketenes which undergo a [2 + 2] cycloaddition reaction to yield tricyclic β-lactones which spontaneously decarboxylate to benzofurans.

Scheme I



Scheme II



Sir: Intramolecular [2 + 2] cycloaddition reactions of the ketene function with the carbon–carbon double bond have recently been reported as a powerful synthetic tool for the synthesis of polycyclic compounds. We now report on the intramolecular [2 + 2] cycloaddition reactions of phenoxyketenes to the carbonyl group.[1]

The intermolecular cycloaddition of ketenes to carbonyl compounds is significantly different from the cycloaddition to olefinic compounds. Elevated temperatures, Lewis acid catalysts, or activation of the carbonyl group is usually required for intermolecular ketene carbonyl compound cycloadditions.[2] However, in an appropriate intramolecular cycloaddition of a ketene function with a carbonyl group the proximity of the two functional groups provides a more favorable condition for cycloaddition. We found that the cycloadditions occur readily with both aldehydic and ketone carbonyl groups.

The difunctional compounds used as precursors for the intramolecular cycloadditions were (*o*-carbonylphenoxy)acetic acids. These acids were readily prepared from commercially available *o*-carbonylphenols and α-halocarboxylic acids as illustrated for (*o*-formylphenoxy)phenylacetic acid in Scheme I. Equal molar amounts of salicylaldehyde and α-bromophenylacetic acid in dry THF upon treatment with sodium hydride and refluxing gave a 78% yield of the desired difunctional compound. Yields of 51–78% of the (*o*-carbonylphenoxy)acetic acids were obtained after recrystallization from a mixture of hexane and methylene chloride.

The (*o*-carbonylphenoxy)acetic acids were converted to the corresponding acid chlorides by reaction with 5–8 equiv of oxalyl chloride in benzene at ambient temperature for 4–8 h. The excess oxalyl chloride was removed under vacuum and the crude acid chloride was diluted with dry benzene and very slowly added to a dilute solution of 3 equiv of triethylamine in benzene at reflux. The dehydrochlorination of the acid chloride was evident by the immediate formation of the amine salt. The reaction mixture was refluxed for up to 3–4 h during which time

(1) (a) Snider, B. B.; Hui, R. A. H. F.; Kulkami, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 2194. (b) Marko, I.; Rosmans, B.; Hesbain-Frisque, A.; Dumas, S.; Ghosez, L. *Ibid.* **1985**, *107*, 2192. (c) Snider, B. B.; Hui, R. A. H. F. *J. Org. Chem.* **1985**, *50*, 5167. (d) Brady, W. T.; Giang, Y. F. *Ibid.* **1985**, *50*, 5177.

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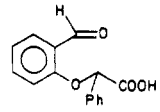
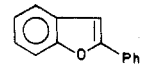
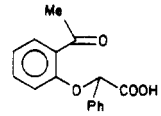
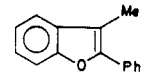
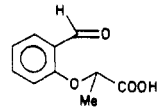
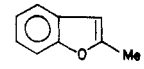
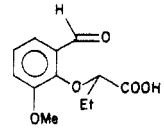
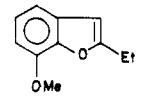
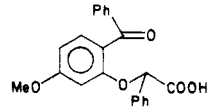
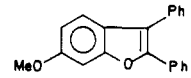
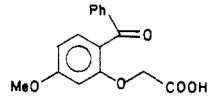
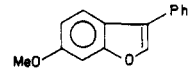
Table I. Intramolecular [2 + 2] Cycloaddition of Ketene and Carbonyl Groups[7]

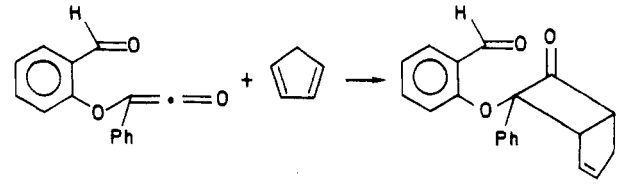
entry	acid	benzofuran	ref	yield, %
1			4a,b	75
2			4b,c,e,f	78
3			5	57
4				53
5				82
6			6	74

carbon dioxide was evolved as evidenced by trapping as the carbonate. We believe this dehydrochlorination resulted in the phenoxyketene which underwent a [2 + 2] cycloaddition reaction with the carbonyl group in the ortho position to yield the β-lactone as illustrated with (*o*-formylphenoxy)phenylacetic acid in Scheme II. The tricyclic β-lactone cycloaddition product spontaneously underwent decarboxylation to yield the benzofuran as evidenced by the elimination of carbon dioxide. The workup simply involved filtration to remove the amine salt and purification by use of a silica gel column (hexane or 0.5% ethyl acetate in hexane). Pure benzofurans were obtained in yields of 53–82% from the corresponding carboxylic acids as illustrated in Table I. Refluxing benzene or toluene may be used as the solvent for the cycloaddition.

It is of interest to note in Table I that unlike intermolecular cycloadditions, there is little difference in whether the carbonyl group is an aldehyde or ketone. To demonstrate the tremendous importance of the proximity effect of the two reacting functions, we attempted the intermolecular cycloaddition of benzaldehyde with (phenoxyphenyl)ketene under the same conditions as described above for the intramolecular cycloadditions. (This is the exact counterpart of entry 1 in Table I.) We found no evidence of the β-lactone or the decarboxylated product, 1,2-diphenyl-1-phenoxyethene; however, a considerable amount of black tar was formed. This result is consistent with that reported by Staudinger.[2d]

The described reaction is very similar to the well-known Perkin reaction for the preparation of benzofuran;[3] therefore, we felt it necessary to demonstrate that these reactions were indeed occurring via ketene intermediates. We were unable to detect the ketene and/or the β-lactone bands in the IR upon examining the spectra of the reaction solutions. However, we have demonstrated the intermediacy of phenoxyketenes in these reactions by trapping the ketene with cyclopentadiene and isolating this cycloaddition product. The [2 + 2] cyclopentadiene adduct of

Scheme III



the phenoxyketene (entry 1 in Table I) has been isolated and characterized by the presence of the carbonyl band in the IR at 1778 cm^{-1} and by analysis of the ^1H and ^{13}C NMR spectra (Scheme III). Furthermore, the Perkin reaction is normally only applicable to aromatic aldehydes and not ketones and of course the present procedure works quite well for ketone carbonyl groups as evidenced by entries 2, 5, and 6 in Table I.

The benzofurans or coumarones have long been known to be widely used in many areas but principally in pharmacology. Most of the syntheses suffer from uncommon starting materials, complicated reaction conditions, poor yields, or lengthy procedures.[4] The synthesis we describe is generally applicable to substituted benzofurans and should serve as a much improved procedure for the preparation of many substituted coumarones.

We are continuing our efforts in the area of intramolecular ketene cycloaddition reactions and are convinced that these reactions will prove to be excellent synthetic routes to various polycyclic compounds.

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(5) Nurunabi, I. B. I. *Pakistan J. Sci. Ind. Res.* **1960**, *3*, 108.

(6) Scherrer, R. A., U.S. Patent 4 022 908, 1977.

(7) Benzofurans from entries 1, 2, 3, and 6 are known compounds and their structures were determined by IR, ^1H and ^{13}C NMR spectral analysis, and comparison of the mp/bp with the literature. Benzofurans from entries 4 and 5 were identified by IR, ^1H and ^{13}C NMR, and satisfactory elemental analysis.

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Reaction of 1,4-Bis(bromomagnesio)pentane and 1,5-Bis(bromomagnesio)hexane with Carboxylic Acid Esters. A Useful, Highly Stereoselective Annelation

Summary: 1,4-Bis(bromomagnesio)pentane and 1,5-bis(bromomagnesio)hexane have been prepared in TFH solution and, when treated with carboxylic acid esters, they afford trans diastereomeric bisubstituted cycloalkanols via a highly diastereoselective intramolecular Grignard reaction.

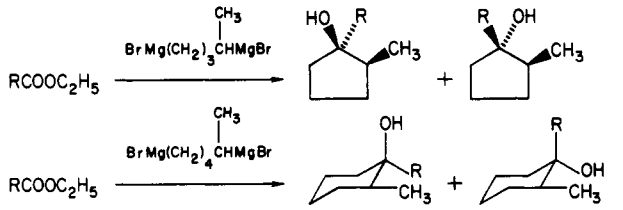
Sir: We have previously reported a versatile one-step synthesis leading to high yields of 1-substituted-cycloalkanols,[1] 1-(ω-hydroxyalkyl)cycloalkanols,[2] and spirolactones.[3] The crucial step is the reaction of α,ω-diprimary di-Grignard reagents with carboxylic acid esters, lactones, and cyclic anhydrides. The results lead to the conclusion that cyclization to a five or a six membered ring is favored over the many possible intra- and intermolecular reactions. Under normal dilution conditions, 1,4-bis(bromomagnesio)butane yields no product arising from intramolecular reduction or enolization when treated with hindered esters.[1] Experiments aimed at seven-membered ring diols[4] and spirolactones showed that dilution does not augment the yields which at best were very low.

The use of 1,3-bis(bromomagnesio)propane with the same series of cyclic anhydrides (mentioned above) gave the corresponding four-membered spirolactones[5] but in lower yields than those reported by Bickelhaupt for the reaction of this di-Grignard with carbon dioxide.[6]

Following our success with the diprimary reagents, we have now prepared some primary–secondary bis-Grignard reagents to follow their reactions with carboxylic acid derivatives particulary because this annelation should enable one to determine the factors which control diastereoselection in intramolecular Grignard reactions.

The primary–secondary bis-Grignards **1** and **2** were prepared from the readily available dibromides[7] in THF solution in yields of 80% and 85% by using the procedure established for the diprimary reagents. Treating these reagents with a series of carboxylic acid esters should reveal if the size of the ring being formed would influence the diastereomer distribution. (Scheme I). The results (Table I) show that the annelation is highly stereoselective affording preferentially the *trans*-2-methyl-1-substituted-cyclopentanols, but the structure of the starting ester has a striking effect on the reaction rate and the isomer distribution. The significance of these observations lies in the fact that the *trans*-OH diastereoisomers which are the major products cannot be obtained conveniently by other general routes.[8] The analysis of the diastereomeic products results from ^1H and ^{13}C NMR spectroscopy, gas chromatography, and high performance liquid chromatography. Published data for certain isomeric 2-methyl-1-substituted-cyclopentanols[9] and cyclohexanols[10] arising

Scheme I



Scheme II

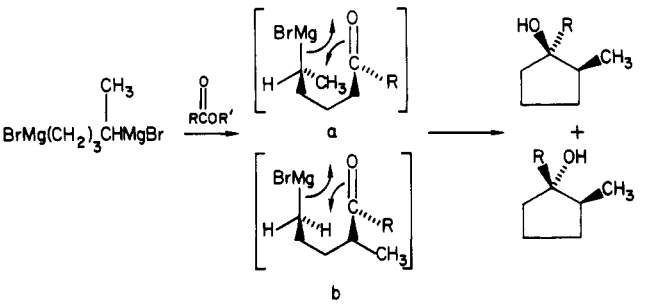


Table I. Reactions of 1,4-Bis(bromomagnesio)pentane with Carboxylic Acid Esters in THF Diastereoisomer Distribution

	2-methyl-1-substituted-cyclopentanols[a,b]		
ester, R	yield (%)	*cis*-OH	*trans*-OH
3, H	**12** 88	23	77
4, CH_3	**13** 77	6	94
5, CH_3CH_2	**14** 76	7	93
6, $C_6H_{11}CH_2$	**15** 81	6	94
7, C_6H_{11}	**16** 75	5	95
8, C_6H_5	**17** 78	11	89
9, *p*-$CH_3C_6H_4$	**18** 70	23	77
10, *p*-ClC_6H_4	**19** 74	18	82
11, *p*-$CH_3OC_6H_4$	**20** 75	40	60

[a] Isolated product. [b] Ratios of diastereomers determined by GC and ^1H NMR.

Table II. ^{13}C NMR Shifts of *cis,trans*-2-Methyl-1-substituted-cyclopentanols

	HO R, CH3		R OH, CH3	
R	δ(CH_3)	δ(C-1)	δ(CH_3)	δ(C-1)
H	13.68	76.02	18.29	80.41
CH_3	12.51	80.63	18.14	81.07
CH_3CH_2	12.59	82.31	16.54	84.22
$C_6H_{11}CH_2$	12.58	82.46	16.61	84.44
C_6H_{11}	12.58	84.29	17.49	87.00
C_6H_5	12.00	83.85	18.29	85.90
p-$CH_3C_6H_4$	12.07	83.34	18.36	85.75
p-ClC_6H_4	12.00	83.70	18.22	85.54
p-$CH_3OC_6H_4$	12.07	83.56	18.31	85.80

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