Polymer-Bound Carbonic–Carboxylic Anhydride Functions. Preparation, Site–Site Interactions, and Synthetic Applications

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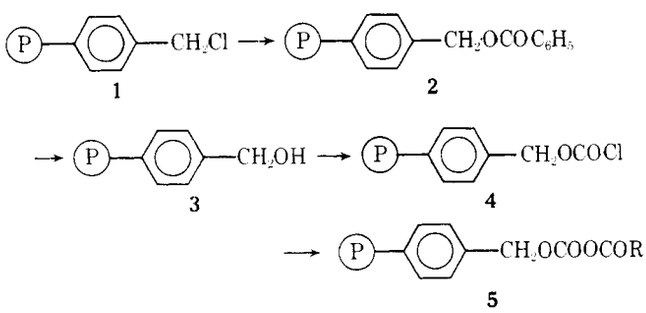
Polystyrene resin beads bearing chloroformate functions ($-CH_2OCOCl$) were prepared and converted to their mixed carbonic–carboxylic anhydride ($-CH_2OCOOCOR$) forms by the addition of a solution of the carboxylic acid (RCOOH) in the presence of a tertiary amine. Quinoline caused the least decomposition of the chloroformate moieties and was used to prepare polymer-bound carbonic phenylacetic anhydrides. The resin bearing the mixed anhydride of acetylsalicylic acid was used to prepare various amides and the symmetrical anhydride. Two decomposition pathways of the resin-bound carbonic benzoic anhydride were investigated under various conditions. Intrastrand reaction resulted in the formation of the benzoate ester on the resin, while interstrand gave the benzoic anhydride and polymeric carbonate. The latter pathway was favored in solvent-swollen resin and the former in dry resin.

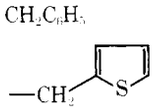
Mixed carbonic–carboxylic anhydrides, R'OCOOCOR, are known to acylate amines under very mild neutral conditions and have found applications in the syntheses of peptides[2] and semisynthetic antibiotics.[3] They are generally considered to be unstable compounds and are prepared in situ just before use. Although Tarbell et al. have shown that many of the high molecular weight anhydrides possess good stability,[4] the same authors found that the benzoic benzylcarbonic anhydride, $C_6H_5COOCOOCH_2C_6H_5$, decomposed rapidly at 0 °C and could not be isolated.[5] Hence we were surprised to find that the same function can be readily created on an insoluble polystyrene support.[6] The resulting resin exhibited good shelf stability and acylating ability for simple and complex amines.[7] Due to the extreme simplicity in the workup procedures allowed by the use of insoluble polymeric reagents,[8] an investigation of the general method of synthesis, stability, and applicability of insoluble resins bearing the mixed carbonic–carboxylic anhydride functionality was undertaken. As the N-acylation of 7-aminocephalosporanic acid (7-aca) by phenylacetic and thiopheneacetic acids leads to commercially significant cephalosporin antibiotics, a major part of the investigation was to find general methods for creating the mixed carbonic anhydrides of these biologically important acids on insoluble supports.

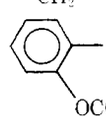
Scheme I



A. R = C_6H_5

B. R = $CH_2C_6H_5$

C. R = 

D. R = 

Results

The reaction sequence leading to the formation of the carbonic benzoic anhydride functions on polystyrene support is shown in Scheme I. Chloromethylpolystyrene (**1**, 2.6 mequiv of chlorine/g) was converted to the benzoate (**2**) and by base hydrolysis to the polymeric benzyl alcohol[9] (**3**). Treatment with excess phosgene converted the alcohol to the chloroformate[9] (**4**, 2.5 mequiv of Cl/g). Addition of a toluene solution of benzoic acid and triethylamine (10% excess in each) at 0 °C resulted in the formation of carbonic benzoic anhydride functions on the resin[6] (**5**, R = C_6H_5; 1.3 mequiv of benzoic acid/g recovered after exhaustive base hydrolysis). Mixed carbonic–carboxylic anhydrides of cinnamic, *p*-chlorobenzoic, thiophene-2-carboxylic, and acetylsalicylic acids were prepared on the polystyrene resin by an identical procedure.

When **4** was treated with a solution of phenylacetic acid and triethylamine under similar conditions, the IR spectrum of the resin showed no appreciable absorption at 1740 cm^{-1}, indicating little, if any, formation of the corresponding anhydride functions (**5B**). Longer reaction time at 0 °C resulted in the loss of the chloroformate functions and no anhydride formation. It seemed likely that the chloroformate functions of **4** were decomposed by triethylamine before any anhydride formation could take place. As the presence of a tertiary amine was essential for the formation of the anhydride functions, a study of the stability of **4** in the presence of various such amines was undertaken. To a suspension of resin **4** in dioxane at 25 °C, equivalent amounts (based on the chloroformate functions) of three tertiary amines were added. The resins were analyzed periodically by IR and elemental analysis. Pyridine and triethylamine caused complete destruction of the chloroformate functions within 30 min as evidenced by IR spectroscopy. As the chloride content of the resins was essentially unchanged, it was evident that the chloroformate functions were being converted to the chloromethyl functions, i.e., resin **1** was being formed from **4**. This was confirmed by further conversion of the resulting product to the benzoate functions (resin **2**). Quinoline, on the other hand, did not cause any appreciable decomposition, as the IR spectrum of **4** remained essentially unchanged even after 6 h.

Resin **4** was subsequently treated with a 15% excess of a benzene solution of phenylacetic acid and quinoline at 25 °C for 2 h. The IR spectrum of the product resin exhibited the typical anhydride doublet at 1740 and 1795 cm^{-1}, indicating the formation of the desired carbonic phenylacetic anhydride functions (**5B**). The formation of *N*-(*n*-propylphenyl)acetamide after the addition of *n*-propylamine showed that the resin contained 1 mequiv/g of phenylacetic acid mixed anhydride. Attempts to prepare carbonic thiophene-2-acetic

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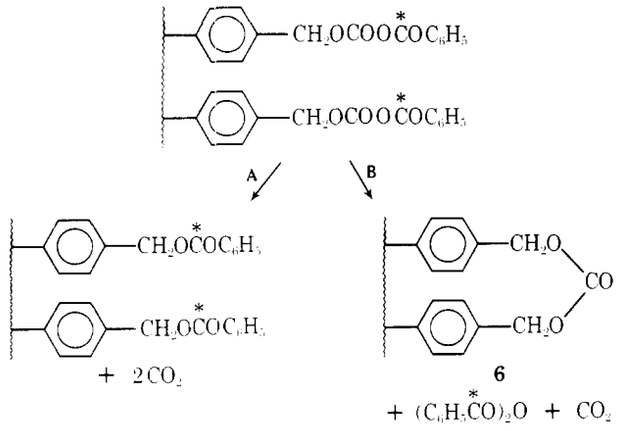
Scheme II



anhydride functions (**5C**) by the same method were generally not successful as low yields of these functions (0.2 mequiv/g) were obtained.

Although the carbonic benzoic anhydride functions anchored to an insoluble support possessed much better stability than their solution-phase monomeric counterparts, the acylating ability of the resin was found to decrease by about 10% after a month of storage at room temperature. Treatment with tertiary amines or heat also resulted in rapid loss in acylating capacity. Tarbell et al. have studied the decomposition of a number of carbonic–carboxylic anhydrides in solution under various conditions and have shown that these functions are destroyed by two major pathways.[5] One is the monomolecular disproportionation by the corresponding ester with loss of carbon dioxide. The other is a bimolecular reaction resulting in the formation of the corresponding symmetrical anhydride, carbonate, and carbon dioxide. The decomposition of the resin-anchored functions by these two pathways is illustrated in Scheme II. To facilitate the study of the breakdown of resin-bound benzoic anhydride functions, resin **5** was synthesized using [7-^{14}C]benzoic acid (resin **5A***). It was shown earlier that these functions react with *n*-propylamine at 25 °C to form the amide quantitatively.[6,12] Hence the release of carbon-14 activity to the solution by the amine was taken as a measure of resin-bound anhydride functionality. Polymeric carbonate functions similar to those on resin **6** do not react with *n*-propylamine under the same conditions. This was shown by synthesizing the benzyl carbonate functions on the resin by the reactions shown in Scheme III. The spectrum of resin **7** exhibited the typical carbonate absorption at 1720 cm^{-1}, which remained unchanged upon treatment with excess *n*-propylamine at 25 °C in dioxane. However, upon reflux the carbonate absorption (of the same reaction mixture) was replaced by the carbamate absorption at 1700 cm^{-1}. Elemental analysis of the resin after complete washing showed the presence of nitrogen, indicating the formation of resin **8**. The benzoate ester functions on resin **2** showed no reaction with *n*-propylamine in refluxing dioxane. A quantitative estimation of the benzoate functions was obtained by exhaustive KOH

Scheme III

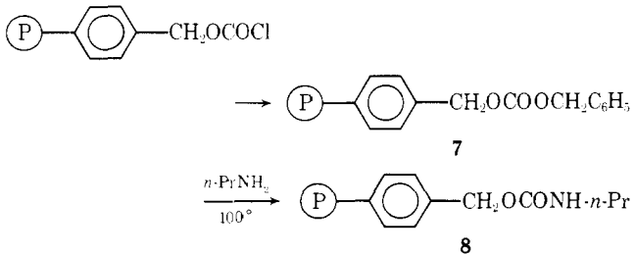


Table I. Fate of Polymer-Bound Carbonic-Benzoic Anhydride Functions (Resin 5A*) Following Various Treatments[a]

treatment	% undecomposed	% conversion to ester (pathway A)	% conversion to carbonate and benzoic anhydride (pathway B)
stored at 25 °C for 1 year	12	68	20
100 °C for 10 h (dry)	16	59	25
90 °C in dioxane (10 h)	1	15	84
37 °C in dioxane with triethylamine (15 h)	1	17	82

[a] Results within ±2%.

hydrolysis in dioxane–water medium followed by determination of the benzoic acid released in solution.

Resin **5A*** was subjected to four treatments as shown in Table I. It was then washed with dioxane, the carbon-14 activity released was measured, and the amount of benzoic anhydride formed (pathway B) was calculated. The washed resin was treated with *n*-propylamine in dioxane at 25 and 100 °C. The activity released after these treatments was measured and the nitrogen content of the resin was determined. These measurements permitted calculation of the unreacted anhydride as well as the newly formed carbonate functions. The resin was subsequently subjected to base hydrolysis and the activity in solution was measured to determine the percent ester formation. The percent anhydride decomposed by pathways A and B (Scheme II) was determined and is shown in Table I.

Reactions on insoluble polystyrene resins are usually performed in nonpolar solvents which readily swell the polymer beads. Polar solvents such as alcohols and water are known to make the immobilized functions less susceptible to further reactions.[9] To determine the effect of solvent polarity on the resin-bound mixed anhydride, the resin was suspended in various mixtures of dioxane and water. About 10% excess of *n*-propylamine was added and the solution was analyzed for carbon-14 activity in a scintillation counter. The results are shown in Figure 1 and illustrate that the reaction takes place in a more quantitative and rapid manner in dioxane than in water.

Resins **5A** and **5B** were subsequently used for the N-acylation of 7-aminocephalosporanic acid (7-aca).[7] The resin anhydride of acetylsalicylic acid (**5D**) was utilized to prepare various amides and the symmetrical anhydride of the acid.[6] The resin (1.3 mequiv of acid/g) was suspended in benzene and the appropriate amine (5% less than stoichiometric amount) was added at room temperature. Over 95% yields of the amides of *n*-propyl- and *n*-butylamine were obtained while benzylamine gave an 80% yield of the amide of acetylsalicylic acid (yields based on the amine). The symmetrical anhydride was isolated in 80% yield after the addition of a benzene solution of an equivalent amount of the acid to resin **5D** in the presence of a tertiary amine.

Discussion

One of the several advantages claimed by many solid-phase practitioners is the "matrix isolation" of the reactive sites immobilized on the polymer supports.[11] In contrast, many workers have shown that site–site interactions on functionalized polystyrene take place even at low levels of resin substitution[12] and high levels of cross-linking.[13] We have found little evidence for the cyclic carbonate formation by interstrand interactions of the polymeric alcohol functions in the preparation of the chloroformate **4** from the alcohol **3**. The

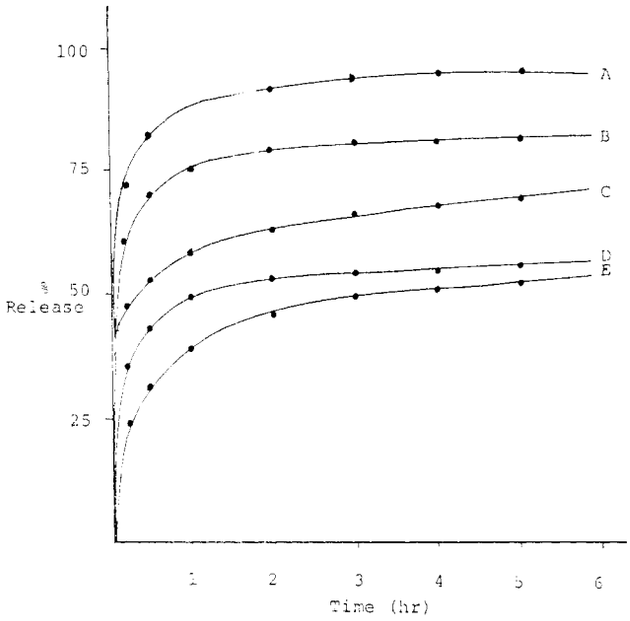


Figure 1. Aminolysis of **5A*** with *n*-propylamine in (A) 100% dioxane, (B) 75% dioxane + 25% water, (C) 50% dioxane + 50% water, (D) 25% dioxane + 75% water, (E) 100% water.

chlorine content of **4** was as expected and the spectrum exhibited no peak at 1720 cm^{-1} for the carbonate. But the evidence clearly showed that site–site interactions between the carbonic benzoic anhydride functions do not take place even under the conditions of low polymer chain mobility (dry condition) and become predominant in the solvent-swelled state. Thus, when resin **5** was stored for a prolonged period or heated to 100 °C in the dry state, about 20% of the immobilized anhydride functions decomposed by the intrastrand pathway A (Scheme II) and the rest by interstrand pathway B. The situation was reversed when the resin was suspended in a solvent, as the majority decomposed by pathway B, the site–site reaction (Table I). This must be due to the high polymer chain mobility allowed by the solvent-swollen state.[15] Therefore, it is reasonable to believe that the mixed anhydride prepared from benzoic acid and benzyl alcohol would decompose mainly via pathway B as the intermolecular reactions can take place freely in solution. Unfortunately this particular anhydride is too unstable to be prepared in solution.[5] Hence, its decomposition pattern in solution could not be compared with that in the polymer-bound form. This phenomenon illustrates the advantage of creating functions on a polymer support as it allows the study of moieties unstable in solution. Recently it has been shown that benzyne intermediates, which are extremely unstable in solution, have much longer half-lives in the polymer-bound state.[14]

The decomposition of many mixed anhydrides in solution has been studied by Tarbell et al.[4] These authors found the decomposition dependent upon the nature of the alcohol and acid components and catalyzed by tertiary amines. Our studies show that in the case of polymer-bound anhydrides **5**, the decomposition was highly dependent upon the nature of R, the carboxylic acid component. Thus, the mixed anhydride of benzoic acid (**5A**) was stable in the presence of quinoline, while that of phenylacetic acid (**5B**) decomposed rapidly under the same conditions. Thus, during the time required to convert all the chloroformate functions (**4**) to the mixed anhydride of phenylacetic acid, appreciable decomposition of the newly formed anhydride functions had taken place. Hence, the reaction was not allowed to proceed to completion. As a consequence, the anhydride resin **5B** possessed some chloroformate functions. This resulted in the lower yields in the N-acylation of *tert*-butyl 7-aminocephalosporinate (based on the amine), as some amine was lost due to binding to the resin as the carbamate. The anhydride of thiophene-2-acetic acid was even less stable and could not be prepared on the resin to be of any practical utility as the acylating agent. When a solution of this acid and quinoline was added to a suspension of the chloroformate resin **4**, periodic IR examination of the resin showed a reduction in the chloroformate absorption at 1765 cm^{-1} with simultaneous increase in the absorption at 1710 cm^{-1} for the corresponding ester and cyclic carbonate **6**. Only a small absorption at 1735–1740 cm^{-1} was observed for the mixed anhydride of thiophene-2-acetic acid.

Results illustrated in Figure 1 show that the polymer-bound anhydride can acylate a simple amine (*n*-propylamine) even in a nonswelling solvent such as water. The reaction proceeded much more rapidly in dioxane, a solvent of good swelling ability for polystyrene beads. Use of benzene gave results similar to those obtained with dioxane.

The synthesis of the amides and anhydride of acetylsalicylic acid in good to excellent yield using **5D** shows the potential of the method for the preparation of derivatives of carboxylic acids with other functionalities. Work is in progress to prepare resins with the mixed anhydride function that swell in aqueous medium. Other polymeric alcohols besides **3** are also being utilized to create the anhydride functions in an attempt to increase the stability of the acylating resins.

Experimental Section

General. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 567 using KBr pellets. NMR spectra were recorded on a Varian EM-360 spectrometer. Radioactive samples were counted in a Hewlett-Packard Model 3375 Tricarb liquid scintillation counter. The stability and reactivity studies of the polymer-bound functions were carried out in a gyrotary waterbath shaker, Model G-76, New Brunswick Scientific, operating at 240 rpm. The solvents were purified and dried by conventional means.

Preparation of 1. The chloromethylated resin was prepared according to the procedure described earlier.[17]

Preparation of 2, 3, and 4. To a solution of 40 mmol of potassium benzoate and a catalytic amount (0.5 mL) of triethylamine in 100 mL of 2-methoxyethanol 12.0 g (31 meq chlorine) of **1** was added. The mixture was refluxed for 4 h. The benzoate resin (**2**; IR 1710 cm^{-1}; 14 g) was washed by decantation with two 200-mL portions of hot 2-methoxyethanol and transferred to a flask containing 60 mmol of potassium hydroxide in 100 mL of 2-methoxyethanol. The mixture was refluxed for 6 h. The alcohol resin (**3**; IR 3420 cm^{-1}; 11 g) was recovered by filtration and washed completely with water and acetone. The dry resin was added to a 75-mL 12.5% solution of phosgene in benzene at 0 °C. After 2 h at 25 °C, the polymer beads (**4**; 12.5 g; IR 1765 cm^{-1}; 2.5 mequiv of Cl g^{-1}) were isolated by filtration, washed well with benzene, and dried.

Preparation of Polymeric Mixed Anhydrides 5A, 5A*, 5B, and 5D. To 10.0 g (25 mequiv of Cl) of **4** in 50 mL of toluene was added 30 mmol of the desired carboxylic acid and 30 mmol of the necessary tertiary amine in 20 mL of toluene. In the preparation of **5A** and **5A*** triethylamine was added and the reaction was allowed to proceed at 0 °C for 30 min. For **5B** quinoline was added and the reaction was conducted at 25 °C for 2 h. In the synthesis of **5A*** the unlabeled acid was spiked with 20 μCi of [7-^{14}C]benzoic acid. The resins were collected by filtration and washed with toluene, dioxane, dioxane–water, dioxane, and ether. Upon base hydrolysis, **5A** and **5B** yielded 1.3 mequiv g^{-1} of benzoic and acetylsalicylic acid and 1 mequiv g^{-1} of phenylacetic acid, respectively. Resin **5A*** was also subjected to base hydrolysis. Total radioactivity of resin **5A*** was found to be 2.15×10^6 cpm g^{-1} when the basic extracts and the washings were counted.

Preparation of 7 and 8. To a solution of 6 mmol of benzyl alcohol and 6 mmol of quinoline in 10 mL of benzene was added 1 g of **4**. The mixture was maintained at 55 °C for 2 h. The resin **7** (1.3 g; IR 1720 cm^{-1}) was collected by filtration and washed with benzene, dioxane, water, acetone, and ether. It was resuspended in 10 mL of benzene and 4 mmol of *n*-propylamine in 5 mL of benzene was added. After refluxing for 4 h the resin **8** was collected by filtration and washed as above for **7** (1.05 g; IR 1700 cm^{-1}).

Stability Studies on 4. Resin **4** (0.25 g each) was added to three solutions containing 1 mmol of triethylamine, pyridine, or quinoline in 50 mL of dioxane. The mixtures were placed in a gyrotary water-

bath shaker at 25 °C operating at 240 rpm. About 0.01-g resin samples were withdrawn periodically, washed with dioxane and ether, and examined by IR spectroscopy (4% KBr pellets) as well as for chlorine content by microanalysis.

Studies on the Decomposition of 5A*. Resin **5A*** was washed completely with dioxane until no radioactivity was detected in the washings. Dry samples of the resin (0.25 g) were subjected to the treatments shown in Table I using 50 mL of dioxane where appropriate. Aliquots of the solution (0.1 mL) were examined periodically for carbon-14 activity. The resins were isolated by filtration, washed, and resuspended in 50 mL of dioxane. A solution of 1 mmol of *n*-propylamine in 10 mL of dioxane was added and the mixtures were shaken at 25 °C for 4 h. The resins were isolated by filtration and analyzed by IR spectroscopy and nitrogen content. Radioactivity in solution was also measured. The amine treatment was repeated at 100 °C for 4 h and the solutions as well as the resins were analyzed in a similar manner.

Reactions of 5A* and *n*-Propylamine in Dioxane–Water. A 0.25-g sample of **5A*** was placed in each flask containing 50 mL of five combinations of dioxane–water (100:0; 75:25; 50:50; 25:75; 0:100). The flasks were shaken at 37 °C for 1 h and 2 mL of 0.2 M *n*-propylamine in dioxane was added. Aliquots of the solution (0.1 mL) were analyzed periodically for carbon-14 activity.

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Registry No.—1, 1592-20-7; 2, 67738-96-9; 3, 56552-12-6; 4, 67738-98-1; **5A**, 67739-00-8; **5A***, 67739-02-0; **5B**, 67739-04-2; **5D**, 67739-06-4; **7**, 67739-08-6; **8**, 67739-10-0; potassium benzoate, 582-25-2; phosgene, 75-44-5; *n*-propylamine, 107-10-8; benzoic acid, 65-85-0; phenylacetic acid, 103-82-2; acetylsalicylic acid, 50-782; [7-^{14}C]benzoic acid, 1589-66-8; benzyl alcohol, 100-51-6.

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Synthesis of Phenyl Enol Ethers via Decarboxylation of β-Lactones Derived from the Lithium α-Phenoxy-α-lithioacetate Synthon

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The lithium α-phenoxy-α-lithioacetate reagent was prepared from α-phenoxyacetic acid by direct α-lithiation with lithium diisopropylamide (LDA) at −78 °C in THF. Condensation of this versatile enolate carboxylate with aldehyde or ketone electrophiles afforded the corresponding β-hydroxy acids in high yield (~80%). β-Lactonization of these β-hydroxy acids with benzenesulfonyl chloride and subsequent decarboxylation led to the desired phenyl enol ethers. This convenient synthetic sequence was shown to be general for alkyl- and aryl-substituted derivatives of phenyl enol ethers.

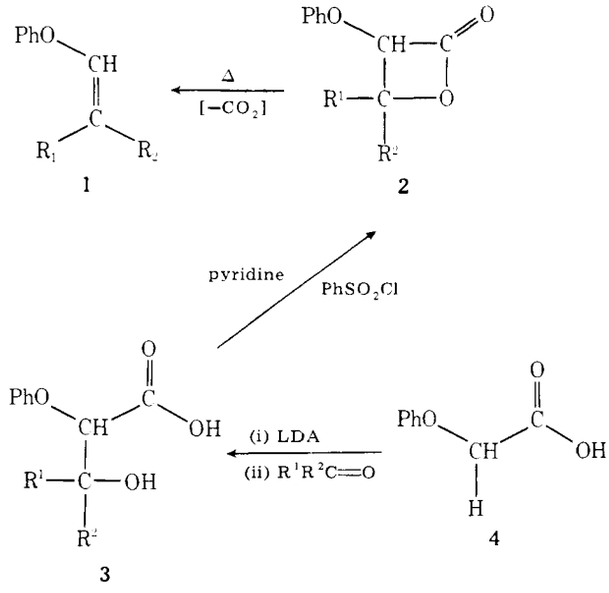
The synthesis of enol ethers **1**, especially aryl enol ethers, is still a cumbersome task. Thus, while silyl enol ethers are readily accessible by silylation of enolates with silyl chlorides,[3] reaction with alkyl halides gives mixtures of carbon and oxygen alkylated products which are difficult to separate. Direct arylation of enolates is not feasible.

Among the more successful methods figures the Wittig reaction (eq 1).[4] An alkoxymethylenephosphorane serves as synthon.

$$\mathrm{ROCH{=}PPh_3} + \mathrm{O{=}CR^1R^2} \longrightarrow \underset{\mathbf{1}}{\mathrm{ROCH{=}CR^1R^2}} + \mathrm{Ph_3P{=}O} \quad (1)$$

The shortcomings of this synthetic approach are the carcinogenicity[5] of the halomethyl ethers which serve as the starting materials for the Wittig reagent, the strongly basic conditions, and the lack of stereospecificity.

Previously[6] we demonstrated that β-lactones serve as convenient and efficient synthons for the stereospecific introduction of double bonds by thermal decarboxylation. This synthetic strategy could be adapted into a useful synthesis of



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