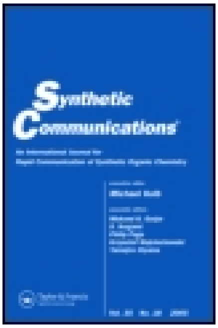

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# Synthesis of Enol Lactones Under a Solid/Liquid Phase Transfer Witting Reaction

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# SYNTHESIS OF ENOL LACTONES UNDER A SOLID/LIQUID PHASE TRANSFER WITTIG REACTION

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**Abstract:** A variety of enol lactones can be prepared through simple and inexpensive solid/liquid phase Wittig condensations of cyclic anhydrides with phosphonium salts.

Enol lactones exhibit a wide range of biological properties, from potent antibiotic to highly desirable odoriferous compounds (1) and are versatile synthons in the construction of other molecules of biological importance (2). The most direct approach to the synthesis of these compounds is through Wittig reactions between stabilized phosphoranes and five-member cyclic anhydrides, and a variety of enol lactones were prepared in this manner (3-9).

In recent years, several reports of Wittig reactions between aldehydes or ketones and phosphonium salts (corresponding to non-stabilized, moderated and stabilized ylides) under solid/liquid phase transfer conditions have appeared in the literature (10-12).

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In this communication we describe the preparation of enol lactones through condensations of cyclic anhydrides with phosphonium salts in the presence of $K_2CO_3$ and LiBr under heterogeneous solid/liquid phase transfer conditions. These condensations are less expensive than conventional Wittig reactions and give excellent yields of enol lactones.

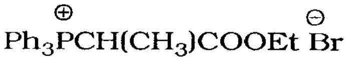
The reactions of several phthalic, maleic and succinic anhydrides with (carbomethoxymethyl)triphenylphosphonium bromide **1** in the presence of $K_2CO_3$ and LiBr were studied and the results are shown in Table 1. The condensations with two other phosphonium salts, (carbomethoxyfluoromethyl)triphenylphosphonium bromide **2** and (carboethoxyethyl)triphenylphosphonium bromide **3** were also investigated and are listed in Table 2.


$\overset{\oplus}{Ph_3P}CH_2COOMe\ \overset{\ominus}{Br}$

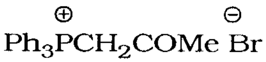
**1**


$\overset{\oplus}{Ph_3P}CHFCOOEt\ \overset{\ominus}{Br}$

**2**


$\overset{\oplus}{Ph_3P}CH(CH_3)COOEt\ \overset{\ominus}{Br}$

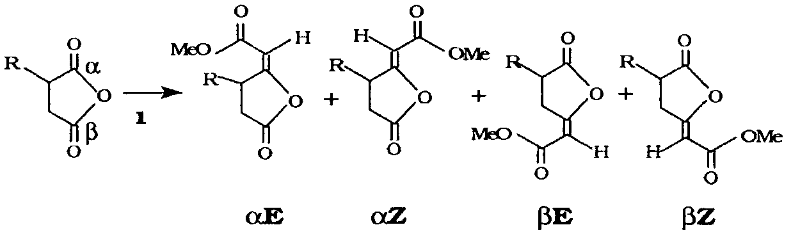
**3**


$\overset{\oplus}{Ph_3P}CH_2COMe\ \overset{\ominus}{Br}$

**4**

The physical properties and spectroscopic data for all enol lactones listed are identical with those reported in the references cited in Table 1.The structures of enol lactones and ratios of isomeric products were determined by $^1H$ NMR spectroscopy (3, 13). For example, in monosubstituted maleic anhydrides, the presence of a highly deshielded proton :CH (8.0 - 8.6 ppm) was used to identify the ßE isomers. The magnetic anisotropic effect of the ylidene ester carbonyl function on the vinylic H is the source of the observed downfield shift (3, 13). Similarly the ßE enol lactones from the phthalic anhydride series could be readily identified by the presence of a doublet of doublets (J = 8 and 2 Hz) for the ortho-H which is shifted downfield, by approximately 1.0 ppm relative to other aromatic protons, due to the

Table 1. Condensations of Phosphonium Salt 1, with CyclicAnhydrides under Solid/Liguid Phase Transfer Conditions



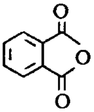
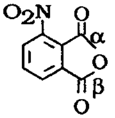
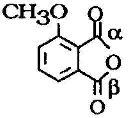
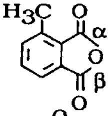
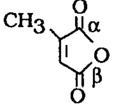
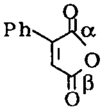
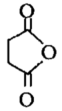
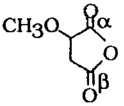
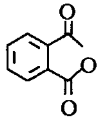
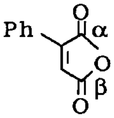
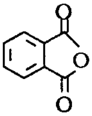
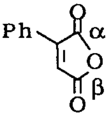
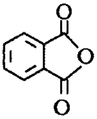
| Anhydride | React. Time (hrs) | Product Distribution | | | | Total Yield (%) | Yield from conventional reaction (ref) |
|---|---|---|---|---|---|---|---|
| | | αE | αZ | βE | βZ | | |
|  | 6 | 80 | 20 | - | - | 56 | 65% (8) |
|  | 6 | 15 | 42 | 34 | 9 | 77 | 82% (7) |
|  | 6 | 7 | 50 | 29 | 14 | 78 | 76-82% (7) |
|  | 6 | - | - | 58 | 42 | 83 | 78% (7) |
|  | 6 | - | 5 | 95 | - | 62 | 84% (6) |
|  | 6 | - | - | 100 | - | 81 | 85% (6) |
|  | 10 | 60 | 40 | - | - | 42 | 45% (5) |
|  | 6 | 100 | - | - | - | 78 | 71% (8) |

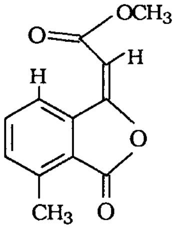
Table 2. Condensations of Phosphonium Salts **2**, **3** and **4** with Cyclic Anhydrides under Solid/Liquid Phase Transfer Conditions

| Anhydride | Salt | React. Time (hrs) | Product Distribution | | | | Total Yield (%) | Yield from conventional reaction (ref) |
|---|---|---|---|---|---|---|---|---|
| | | | αE | αZ | βE | βZ | | |
|  | 3 | 15 | 91 (E) | 9 (Z) | | | 90 | 61% (15) |
|  | 3 | 12 | - | - | 100 | - | 92 | 93% |
|  | 2 | 6 | 100 (Z) | | | | 92 | 71% |
|  | 2 | 6 | - | - | 100 (Z) | | 52 | 50% |
|  | 4 | 12 | 100 (E) | | | | 87 | 65% (15) |

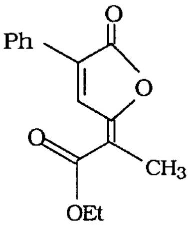
effect of the neighbouring ylidene carbonyl group. The NMR data are supported by X-ray crystal structure of compound **5** (14), where ßE configuration matches the assigned $^1$H NMR. The assignment of structures was confirmed by the isomerisation experiments (13).

Of the cases that were not reported previously in the literature (Table 2), the condensation of phenyl maleic anhydride with **3** gave a single product with a signal for the vinylic proton at 8.47 ppm, identifying it as **6ßE**.

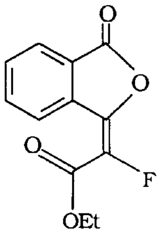
The condensation of phthalic anhydride with **2**, under phase transfer conditions, gave a single product **7**(Z) in 92 % yield. The stereochemistry of this compound was deduced by the presence of a highly deshielded signal for an aromatic proton at 8.90 ppm. Phenylmaleic anhydride reacted with **2** to give after 6 hours of reflux only enol lactone **8β**(Z) with a characteristically deshielded vinylic proton at 8.40 ppm. When the reflux was continued for additional several hours **8β**(Z) was isomerised partially to **8β**(E). After 14 hours of reflux the mixture consisted of **8β**(Z) : **8β**(E) in the ratio of 40 : 60 (total yield 83%). The spectroscopic data for all new condensation products are listed in the experimental section.



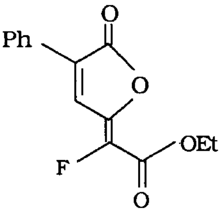
**5 β E**



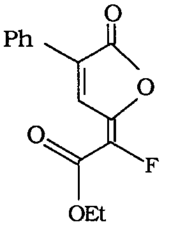
**6 β E**



**7 (Z)**



**8 β E**



**8 β Z**

General procedure for the condensation reactions is outlined in the experimental section. In order to maximize yields of enol lactones, it is important to remove any acidic contaminants from cyclic anhydrides. The procedure for the purification of cyclic anhydrides is as follows: crude anhydride dissolved in freshly distilled acetyl chloride is refluxed for 3 hours. After removing acetic acid and the remaining acetyl chloride by distillation under reduced pressure, the anhydride is placed in a vacuum desiccator over KOH for several hours. The anhydrides are crystallized from dry chloroform.

As in conventional Wittig reactions, solid/liquid phase transfer reactions with maleic and phthalic anhydrides require shorter times and give better yields than the corresponding reactions with succinic anhydrides. Methoxysuccinic anhydride is an exception; under conventional as well as phase transfer conditions it reacts at a rate comparable to that of unhindered maleic anhydrides and gives an excellent yield of the pure αE isomer.

The solid/liquid phase transfer reactions are particularly favourable with phosphonium salts **2** and **3**, which give higher yields and purer products than the corresponding reaction with the prepared ylides. The condensation of phthalic anhydride with **4** was also carried out successfully, indicating that these reactions are not restricted to the ester substituted phosphonium salts.

The regioselectivities of the condensations with unsymmetrically substituted cyclic anhydrides carried out under solid/liquid phase transfer conditions are identical with those reported for conventional Wittig reactions.

## Experimental Section

**General Procedure:** Phosphonium salt (2 mmol) and cyclic anhydride (2 mmol) were dissolved in anhydrous THF (30 ml) , then anhydrous $K_2CO_3$ (5 mmol) and LiBr (2 mmol) were added in one portion. The mixture was stirred and refluxed for several hours under nitrogen atmosphere. At the end of the reaction ether (20 ml) was added to precipitate most of triphenylphosphine oxide, which was then removed by filtration. The remaining solution was concentrated and the products were purified by flash chromatography on silica gel using ether : petroleum ether (1 : 2) as elutant.

Reaction of phenylmaleic anhydride with **3** gave crystalline compound **6βE**, mp. 58-61°; 92% yield; ir ($CHCl_3$) ν $cm^{-1}$ : 1780, 1705, 1645 ; $^1$Hnmr (200MHz, $CDCl_3$) δ: 1.38 (t, 3H ), 2.18 (s, 3H ), 4.31 (q,2H), 7.43-7.45 (m,5H), 8.47 (s,1H); $^{13}$C nmr (50.32Hz,$CDCl_3$) δ: 13.48, 14.27, 61.37, 113.12, 127.52, 128.43, 128.92, 130.31, 132.20, 132.90, 133.66, 154.85, 166.38; ms (EI), m/z: 258 (M ,73.2%), 213 (34.3%), 184 (100%), 102 (83.8%); ms (HR), m/z : Calcd. for $C_{15}H_{14}O_4$ : 258.0892; Found: 258.0891.

Reaction of phthalic anhydride with **2** gave **7**(Z), mp. 78-82; 92% yield; ir ($CHCl_3$) ν $cm^{-1}$ : 1840, 1765, 1700, 1645; $^1$Hnmr (200MHz, $CDCl_3$) δ: 1.45(t,3H), 4.40(q,2H), 7.60-8.10(m,2H), 8.90(d,1H,Z-form); $^{13}$Cnmr (50.32Hz, $CDCl_3$) δ: 14.15, 62.34, 125.32, 126.08, 127.03, 131.91, 135.22, 135.41, 136.95, 143.23, 160.96, 164.32; $^{19}$F δ: -132.57(Z-form); ms (EI), m/z: 236 (M,29%), 164 (51.1%), 148 (40.1%), 104 (100%), 76 (88%); ms (HR), m/z : Calcd. for $C_{12}H_9O_4F$ : 236.0485; Found: 236.0477.

Reaction of phenylmaleic anhydride with **2** gave **8βZ** as crystalline compound, mp. 63-67; 52% yield; ir ($CHCl_3$) ν cm-1: 1845, 1780, 1710, 1640; $^1$Hnmr (200MHz, $CDCl_3$) δ: 1.40(t,3H), 4.30(q,2H), 7.45-7.90(m,5H), 8.40(s,1H); $^{13}$Cnmr (50.32Hz,$CDCl_3$) δ: 14.16, 62.53, 124.53, 127.52, 127.69, 128.52, 129.03, 129.34, 130.45, 130.84, 132.80, 159.24, 160.46; 19F δ: -134.25; ms (EI), m/z: 262 (M,33.1%), 188 (29.3%), 174 (27.5%), 116 (14.9%), 102 (100%); ms (HR), m/z: Cacld. for $C_{14}H_{11}O_4F$ : 262.0641; Found: 262.0629.

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