Reactions of Ketenes. XX [1]. Phenylketene Dimethylacetal As Synthon For the Introduction of Functionalized Phenylethyl Units

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Phenylketene dimethylacetal (**1**) reacts with the α-diazoketones to give the dihydrofurans **6**. These compounds, as cyclic ortho esters, can undergo dealcoholation into the furans **2** and hydrolysis into the γ-ketoesters **3** and into the γ-ketoacids **4**. Cyclopropane acetal **8**, obtained starting from acetal **1** and ethyl diazoacetate, by heating leads quantitatively to functionalized ester **9**. These synthetic methods enlarge the sphere of applicability of the electron-rich alkene **1** as synthon in organic synthesis.

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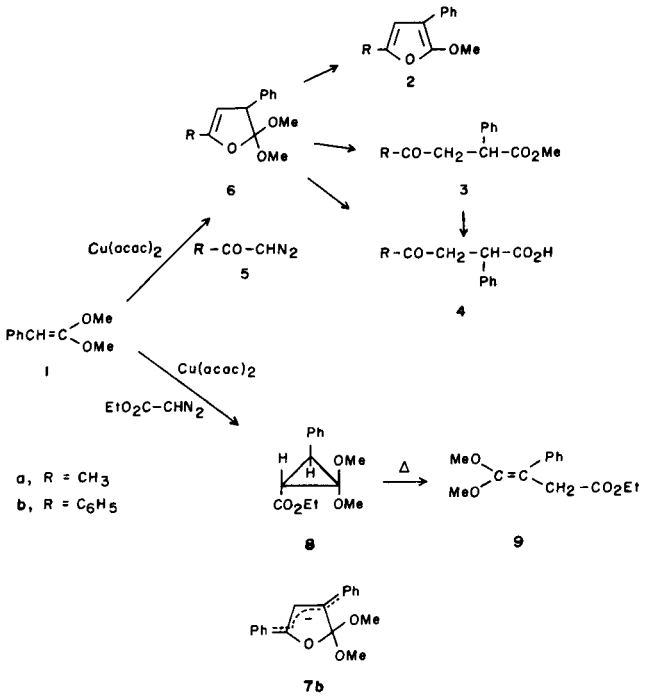
Phenylketene dimethylacetal (2,2-dimethoxyethenylbenzene) (**1**) reacts with benzyl bromide [2], phenylisocyanate [3,4], thiobenzoylisocyanate [5], diphenylketene [6,7] nitrile oxides [8], phenylazide [9], ethyl azidoformate [10-12], azocarboxylate esters [13-15], ethyl diazoacetate [1], to give linear or cyclic *gem*-dimethoxy compounds which owing to the structural features are intermediates in organic synthesis [1-18]. Therefore by use of this electron-rich alkene several compound types were obtained, a functionalized phenylethyl unit being introduced in the skeleton of the molecule of the reactive. It is noteworthy that sometimes the interemediates obtained starting from phenylketene dimethylacetal (**1**) behave differently from the ones deriving from alkylsubstituted or unsubstituted ketene acetals [3,10,12].

As part of a program of study on the sensitized photooxidation of furans [19], we were interested on the synthesis of 2-methoxy-3-phenylfurans **2** and of the phenylfuranones. In connection with the syntheses of the latter it was interesting to obtain 3-acyl-2-phenylpropanoic esters **3** or acids **4** and functionalized 3-phenylbut-3-enoic esters [20].

Among the reported methods for the preparation of 2-alkoxyfurans [21], the aromatization of 2,2-dialkoxy-2,3-dihydrofurans, which we reported several years ago [22], offers a wide range of applicability. However, at that time we did not extend the synthesis to obtain the 3-phenyl derivatives, discouraged by the isolation difficulties of the product of the copper powder catalysed reaction between phenylketene dimethylacetal (**1**) and diazoacetone (**5a**). We have now taken again the matter and, with some clever devices, we have reached the aim. All attempts to isolate the product of the catalysed reaction between the acetal **1** and diazoacetone (**5a**) by chromatographic methods failed since it undergoes hydrolysis on contact with the adsorbents and also in the presence of atmospheric moisture. Therefore we have obtained in 65% yields 2,2-dimethoxy-5-methyl-3-phenyl-2,3-dihydrofuran (**6a**) (identified by ^{1}H nmr spectrum, see Table) as an unseparable mixture together with acetal **1** (*ca.* 30%), by distillation of the mixture of bis(acetoacetonato)copper(II) [Cu(acac)$_2$] [23] catalysed reaction between the acetal **1** and diazoacetone (**5a**). The aromatization of the dihydrofuran **6a**, by removal of methanol, into 2-methoxy-5-methyl-3-phenylfuran (**2a**) was carried out by refluxing the xylene solution of the aforementioned mixture of **6a** and **1** in the presence of aluminium *t*-butoxide, which can function both as base and as Lewis acid [24]. The furan **2a** was isolated by chromatography on silica gel in 68% yields



and identified on the basis of the analytical and spectral data reported in the Table. It is noteworthy that, differently from dihydrofuran **6b** (see below), dihydrofuran **6a** failed to give furan **2a** by treatment with methanolic potassium hydroxide and after this treatment it is recovered unchanged. By the same route used for **6a** but without trouble, starting from acetal **1** and diazoacetophenone (**5b**), 2,3-dimethoxy-3,5-diphenyl-2,3-dihydrofuran (**6b**) was prepared and isolated by distillation in 70% yields. Identifi-

Table

Physical, Spectral, and Analytical Data of the New Products

Product	Mp(°C) or Bp (°C/mmHg)	IR (ν cm^{-1})	^{1}H-nmr (δ ppm, J = Hz)	Formula	Analyses(%) Calcd./Found C	H
6a	oil [a]	1681 [b]	1.94 (3H, dd, J 2.2, 1.2, CH_3), 3.02 and 3.42 (6H, 2s, 2 × OCH_3), 4.04 (1H, dq, J 2.6, 2.2, 3-H), 4.79 (1H, dq, J 2.6, 1.2, 4-H), 7.20-7.40 (5H, m, C_6H_5)			
6b	140-142/0.6	1652 [c]	3.11 and 3.49 (6H, 2s, 2 × OCH_3), 4.25 (1H, d, J 2.9, 3-H), 5.57 (1H, d, J 2.9, 4-H), 7.20-7.70 (10H, m, 2 × C_6H_5)	$C_{18}H_{18}O_3$	76.42 (76.57)	6.25 (6.43)
2a	oil	1640, 1605 1022 [d]	2.23 (3H, d, J 1.1, CH_3), 3.96 (3H, s, OCH_3), 6.17 (1H, q, J 1.1, 4-H), 7.10-7.60 (5H, m, C_6H_5)	$C_{12}H_{12}O_2$	76.60 (76.57)	6.42 (6.43)
2b	85-87	1630, 1601 1015 [d]	4.09 (3H, s, OCH_3), 6.87 (1H, s, 4-H), 7.13-7.68 (10H, m, 2 × C_6H_5)	$C_{17}H_{14}O_2$	81.42 (81.58)	5.66 (5.64)
3a [e]	67-69	1730, 1720 [d]	2.16 (3H, s, CH_3), 2.71 and 3.39 (2H, 2dd, AM part of AMX system, J_{AM} 18.4, J_{AX} 10.4, J_{MX} 4.4, CH_2), 3.65 (3H, s, OCH_3), 4.10 (1H, dd, X part of AMX system, J_{AX} 10.4, J_{MX} 4.4, CH), 7.23-7.40 (5H, m, C_6H_5)			
9	161-163/0.2	1738, 1662 [c]	1.18 (3H, t, J 7.0, CH_3), 3.38 (2H, s, CH_2), 3.53 and 3.63 (6H, 2s, 2 × OCH_3), 4.09 (2H, q, J 7.0, OCH_2), 7.18-7.39 (5H, m, C_6H_5)	$C_{14}H_{18}O_4$	66.92 (67.18)	6.06 (7.25)

[a] Mixture composed of dihydrofuran **6a** and acetal **1** (see Experimental). [b] Neat. [c] Carbon tetrachloride as solvent. [d] Chloroform as solvent. [e] Known product [26], but ir and ^{1}H-nmr data are unreported.

cation was made on the basis of the analytical and spectral data reported in the Table. The aromatization of the dihydrofuran **6b** can be accomplished by heating the compound with methanolic potassium hydroxide. 2-Methoxy-3,5-diphenylfuran (**2b**), identified on the basis of the analytical and spectral data (see Table), is obtained in 82% yields. The different behaviour of the dihydrofurans **6a** and **6b** towards methanolic potassium hydroxide can be easily explained taking into account the high resonance stabilization of the carbanion **7b**, obtained from **6b** in the first stage of the reaction with the base.

The dihydrofurans **6**, as cyclic ortho esters, by acid hydrolysis could be easily transformed into γ-ketoesters or γ-ketoacids. In this connection, it is noteworthy that 3-acyl-2-phenylpropanoic esters and acids, though intermediates in the synthesis of 3-phenyl-2(3*H*)-furanones, are difficult to obtain [20,25]. When we hydrolyzed, under mild conditions, the aforementioned mixture of the dihydrofuran **6a** and of the acetal **1**, a mixture of methyl 4-oxo-2-phenylpentanoate (**3a**) [26] and methyl phenylacetate was obtained, the latter deriving from the acetal **1** hydrolysis. The ester **3a** was isolated by silica gel chromatography (yield 85%) and hydrolyzed under drastic conditions to the γ-ketoacid 4a [25] (global yields of **4a** 79%) [27]. Dihydrofuran **6b** leads, by mild acid hydrolysis, to the γ-ketoester **3b** [25] and, by drastic acid hydrolysis, to the γ-ketoacid **4b** [25]. The already known **4a**, **3b**, and **4b** were identified by comparison of their mp and their ^{1}H nmr spectra with those of authentic samples [25]. The already known **3a** was identified by comparison of its mp with that of authentic sample [26] and on the basis of the spectral data reported in the Table.

As regards the preparation of functionalized 3-phenylbut-3-enoic esters, we have taken into account the possibility to isomerize the thermally unstable ethyl 2,2-dimethoxy-3-phenylcyclopropane-1-carboxylate (**8**), synthesized starting from acetal **1** and ethyl diazoacetate [1,28]. By heating in a sealed ampoule [29] at 180°, cyclopropane **8** yielded quantitatively ethyl 4,4-dimethoxy-3-phenylbut-3-enoate (**9**) which was identified by the analytical and spectral data reported in the Table. Ester **9** is intermediate in a potential synthesis in three steps of 5-methoxy-4-phenyl-2(5*H*)-furanone planed as an alternative pathway to that one previously reported starting from phenylcyclobutadienoquinone [30]. As to the ring opening process of the cyclopropane **8**, it is noteworthy that 2-alkoxycyclopropane-1-carboxylate esters are inert to ring opening at their boiling points [31]. Therefore it is evident that the combination, on the cyclopropane ring, of the two alkoxy groups and of the vicinal carbethoxy substituent which exhibit opposing electron-donor capacities is essential for this rearrangement.

The aforementioned synthetic methods enlarge the sphere of applicability of phenylketene dimethylacetal (**1**) which, also on the basis of the data reported previously in the literature [1-18], must be considered as a synthon for the introduction of functionalized phenylethyl units in organic molecules.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr spectra were recorded with deuteriochloroform as solvent on a Bruker WH 270 spectrometer with tetramethylsilane as internal standard. The ir spectra were measured on a Perkin-Elmer 399 spectrophotometer. Silica gel 0.05-0.20 mm (Merck) and light petroleum bp 30-50° were used for column chromatographies.

2,2-Dimethoxy-5-methyl-3-phenyl-2,3-dihydrofuran (**6a**).

A solution of diazoacetone (**5a**) [32] (10 mmoles) in dry benzene (4 ml)

was added dropwise to a stirred suspension of $Cu(acac)_2$ (4.6×10^{-2} mmole) and phenylketene dimethylacetal (**1**) [33] (20 mmoles) in dry benzene (5 ml) heated at 85°. Upon completion of the addition (60 minutes) the mixture was heated at 85° for a further 30 minutes. After evaporation of the solvent under reduced pressure, the residue was distilled to give at 97-120°/14 mm the most of the excess of the acetal **1** and further at 126-136°/14 mm a mixture composed of dihydrofuran **6a** (70%) and acetal **1** (30%). The ir and ^1H nmr data of the dihydrofuran **6a**, reported in the Table, were obtained from those of the mixture rejecting the signals of the acetal **1**. The yield of **6a** was 65%.

2-Methoxy-5-methyl-3-phenylfuran (**2a**).

The solution in 1 ml of dry xylene of 180 mg of the aforementioned mixture at bp 126-136°/14 mm, containing 140 mg of **6a**, was refluxed after addition of 156 mg of aluminium *t*-butoxide. After 4 hours the reaction mixture was added to 10% sodium hydroxide solution and extracted with ether. The usual work up gave a mixture which was chromatographed over silica gel. Using light petroleum/ether (49:1 v/v) as eluent, pure furan **2a** was obtained in 68% yield. All the procedure must be carried out under nitrogen for furan **2a** oxidizes in the presence of atmospheric oxygen. Physical, spectral and analytical data of the furan **2a** are reported in the Table.

Methyl 4-Oxo-2-phenylpentanoate (**3a**).

A 5% acetone solution of 300 mg of the aforementioned mixture of the dihydrofuran **6a** and acetal **1** at bp 126-136°/14 mm containing 230 mg of **6a**, after addition of 1*N* hydrochloric acid (0.1 ml), was kept at room temperature for 3 hours. Removal of the solvent and chromatography over silica gel using light petroleum/ether (45:1 v/v) as eluent gave 60 mg of methyl phenylacetate deriving from acetal **1**. Elution with light petroleum/ether (9:1 v/v) gave 180 mg (yield 85%) of ketoester **3a**, mp 67-69° (lit [26], mp 69.5-70°); ir and ^1H nmr spectra of the ketoester **3a**, unreported in the literature, are summarized in the Table.

4-Oxo-2-phenylpentanoic Acid (**4a**).

A 10% dioxane solution of the ketoester **3a** (200 mg) after addition of concentrated hydrochloric acid (1 ml) was refluxed for 6 hours. The usual work up gave in 93% yield ketoacid **4a**, mp 126-127° (lit [25], mp 124-127°), identified by comparison (^1H nmr spectrum) with authentic sample [25].

2,2-Dimethoxy-3,5-diphenyl-2,3-dihydrofuran (**6b**).

The $Cu(acac)_2$ catalysed reaction between acetal **1** and diazoacetophenone (**5b**) [34] was carried out as above reported for dihydrofuran **6a**. After evaporation of the solvent under reduced pressure, the residue was distilled to give first the unchanged acetal **1** and further pure dihydrofuran **6b** at bp 140-142°/0.6 mm in 70% yields. Physical, spectral and analytical data of the dihydrofuran **6b** are reported in the Table.

2-Methoxy-3,5-diphenylfuran (**2b**).

A 5% dioxane solution of dihydrofuran **6b** (200 mg) after addition of 2% methanolic potassium hydroxide (4 ml) was refluxed for 4 hours. Removal of the solvents and chromatography over silica gel using light petroleum/ether (19:1 v/v) as eluent gave pure furan **2b** in 82% yields. All the procedure must be carried out under nitrogen for furan **2b** oxidizes in the presence of atmospheric oxygen. Physical, spectral and analytical data of **2b** are reported in the Table.

Methyl 4-Oxo-2,4-diphenylbutanoate (**3b**).

A 5% acetone solution of the dihydrofuran **6b** (300 mg) after addition of 1*N* hydrochloric acid (0.1 ml) was kept at room temperature for 3 hours. Removal of the solvent under reduced pressure and chromatography over silica gel using light petroleum/ether (9:1 v/v) as eluent gave in 83% yield, ketoester **3b**, mp 102-105° (lit [25], mp 103-104°), identified by comparison (^1H nmr spectrum) with authentic sample [25].

4-Oxo-2,4-diphenylbutanoic Acid (**4b**).

A 10% solution of the dihydrofuran **6b** (650 mg) after addition of concentrated hydrochloric acid (3.5 ml) was refluxed for 6 hours. The usual workup gave in 82% yield, ketoacid **4b**, mp 151-153° (lit [25], mp 152-153°), identified by comparison (^1H nmr spectrum) with authentic sample [25].

Ethyl 4,4-Dimethoxy-3-phenylbut-3-enoate (**9**).

The cyclopropane **8** is prepared as previously described [1] by reaction of ketene acetal **1** with ethyl diazoacetate using $Cu(acac)_2$ as catalyst and dry benzene as solvent. After evaporation of the solvent under reduced pressure the residue, which showed (^1H nmr) cyclopropane **8** and butenoate **9** in *ca.* a 6:1 molar ratio, was distilled under reduced pressure to give first the unreacted acetal **1** and further, in 72% yield, a fraction (bp 150-160°/0.2 mm) which was composed (^1H nmr) of cyclopropane **8** and butenoate **9** in *ca.* a 3:2 molar ratio. This fraction was heated at 180° in a sealed ampoule [29]; after 4 hours the ^1H nmr spectrum indicated that cyclopropane **8** was quantitatively converted into butenoate **9**. Physical, spectral and analytical data of **9** are reported in the Table.

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