α-DIKETONES IN [4+2] CYCLOADDITIONS

REACTIONS OF DIMETHYL 2,3-DIOXOSUCCINATE WITH ENOL ETHERS

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Dedicated to Rolf Huisgen on the occasion of his 75th birthday.

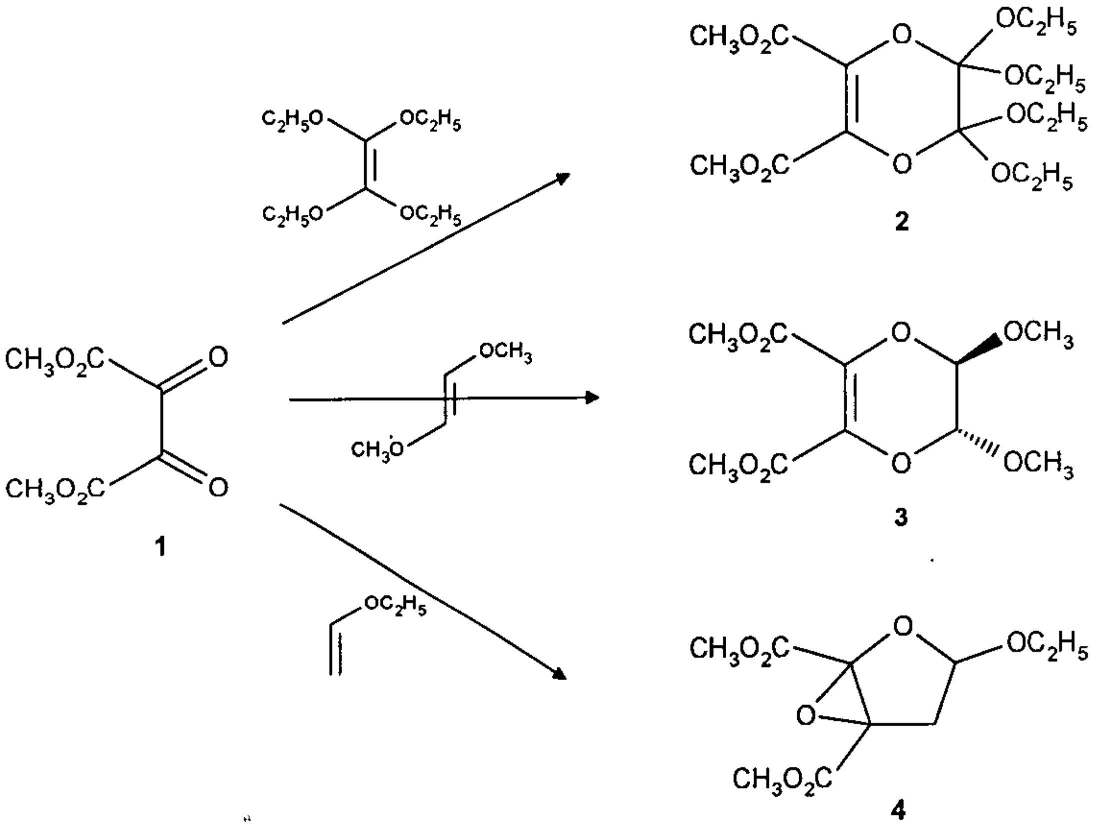
Abstract - Dimethyl 2,3-dioxosuccinate (**1**) undergoes cycloaddition with enol ethers. Dihydrodioxine derivates, products of [4+2] cycloaddition, are formed with tetraethoxyethylene and *E*-1,2-dimethoxyethylene. The stereospecificity of the reaction of **1** with *E*-1,2-dimethoxyethylene suggests a concerted mechanism for this cycloaddition. The polarized double bond of ethyl vinyl ether reacts with **1** to give 4,5-dihydro-2,3-dimethoxycarbonyl-2,3-epoxy-5-ethoxyfuran in a hitherto unknown reaction of 1,2-diketones.

1,2-Diketones can be considered as heterodienes which might undergo [4+2] cycloaddition. A few examples of such reactions were reported.[1,2] Because of the replacement of two C-atoms in 1,3-

butadiene by the more electronegative oxygen atom 1,2-diketones should be suited for Diels-Alder reactions with inverse electron demand.[3] Indeed the reactions known involve mainly enol ethers. In assessing the cycloaddition capability of 1,2-diketones it has to be taken into account that CO double bonds are more stable than CC double bonds and that, for this reason, [4+2] cycloadditions might not be favorable thermodynamically. It is not surprising that *o*-quinones for which the gain of aromaticity provides the driving force belong to the examples which yield dihydro-1,4-dioxines in reactions with *e. g.* enol ethers. The other 1,2-diketones are benzil and acenaphthenequinone[4] where conjugation of the aromatic substituents with the double bond in the dihydrodioxine may compensate for the loss of the CO-π-bond energy. Catalysis by $ZnCl_2$ is necessary in the latter cases. 1,1-Dimethoxy-1-propene with it's highly polarized double bond leads to products of [2+2] cycloaddition, oxetanes and bis-oxetanes, presumably in stepwise reactions.[4] Here we describe yet another 1,2-diketo compound, dimethyl 2,3-dioxosuccinate (**1**),[5] which undergoes cycloaddition with symmetrical and unsymmetrical enol ethers.

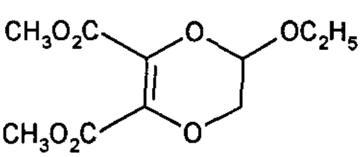
Results and discussion

The reaction of dimethyl 2,3-dioxosuccinate (**1**) with an equimolar amount of tetraethoxyethylene in dichloromethane at room temperature leads to >90 % of cycloadduct (**2**) within 5 min (Scheme 1). Compound (**2**) is characterized spectroscopically. The ^{1}H-nmr spectrum indicates three different groups of protons: a singlet for the two methyl groups of the methoxycarbonyl substituents, a multiplet for the methylene groups and a triplet for the methyl groups of the ethoxy groups. Thus all ethoxy- and the two methoxycarbonyl groups are equivalent. The number of ^{13}C-nmr signals supports the symmetrical structure. At 162.2 ppm an ester carbonyl group and at 130.7 ppm an olefinic C-atom is found. The signal at 108.9 ppm is assigned to the orthoester C-atom, and three more signals at 15.2 (CH_3), 59.7 (CH_2), and 52.5 (CH_3) ppm describe ethoxy and methoxy carbon atoms. The ir spectrum shows the presence of a CC double bond at υ = 1655 cm^{-1} and a carbonyl vibration at 1735 cm^{-1}. The M$^+$ peak of 378 in the mass spectrum confirms the 1:1 adduct. Thus all data are in agreement with **2** as the reaction product. The stereochemistry of the [4+2] cycloaddition was studied with *E*-1,2-dimethoxyethylene. This dienophile, being substituted by only two alkoxy groups reacts slower than tetraethoxyethylene with **1**. Within 20 days at room temperature in dichloromethane a 60 % conversion had been achieved. Besides residual starting material only one product could be detected by ^{1}H-nmr spectroscopy. From the 1.0 Hz coupling for the hydrogen atoms of the former double bond their diequatorial arrangement is delineated which corresponds to retention of stereochemistry at the former double bond and suggests, therefore, a concerted [4+2] cycloaddition. The ^{13}C-nmr and the ir data are in agreement with **3** as the product (see experimental).



Scheme 1

The reaction of benzil with the polarized double bond of 1,1-dimethoxy-1-propene, a ketene acetal, had led to products of [2+2] cycloaddition, an oxetane, respectively a bisoxetane.[4] If **1** and ethyl vinyl ether, which has also a polarized enol ether double bond, are mixed in a 1:1 ratio in dichloromethane a single product (>90 %) is formed in 24 h, as deduced from the ^{1}H-nmr spectrum. According to the M$^+$ peak in the mass spectrum it is a 1:1 adduct. We considered **5** and **6** as possible reaction products, could, however, not confirm one of these structures by the spectroscopic data.



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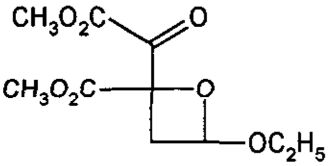

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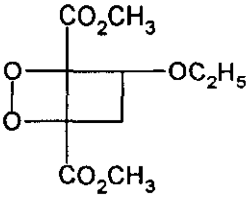

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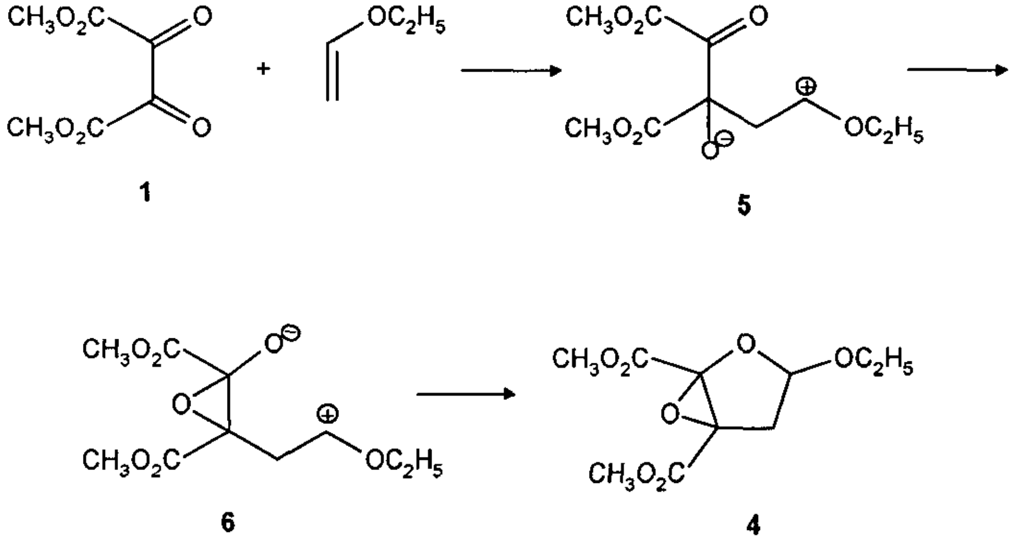
The following spectroscopic observations are made: Two carbonyl vibrations at 1740 cm^{-1}and 1763 cm^{-1}, no CC double bond or α-keto ester vibration in the ir. The ^{1}H-nmr spectrum displays eight different kinds of hydrogen atoms: two ester methyl signals at 3.87 and 3.91 ppm, one methyl group (triplet) at 1.25 ppm, two diastereotopic methylene protons as multiplets at 3.52 and 3.94 ppm. These two protons are bound to the same C-atom as shown by a CH-correlation spectrum. An ABM pattern, 2.48, 2.96 and 5.68 ppm and coupling constants of 1.8, 6.9 and 14.9 Hz derives from the protons at the former CC double bond of the enol ether. The ^{13}C-nmr spectrum shows different chemical shifts for all ten carbon atoms of a 1:1 adduct: two ester methyl signals at 53.5 and 54.1 ppm, two C=O groups at 162.7 and 164.7 ppm. The ethoxy group shows peaks at 14.9 ppm (CH_3) and 65.2 ppm (CH_2). In addition there are a methine carbon atom (107.1 ppm), a methylene C-atom (36.3 ppm), and two quarternary carbon atoms at 68.5 and 88.6 ppm. The ir data exclude structures (**5**) and (**6**) for the isolated compound. In addition the absence of olefinic carbon atoms in the ^{13}C-nmr discredits compound (**5**) as product.

There remain two more possibilities: **4** and **7**. These structures are in agreement with the ir , nmr and analytical data. A distinction between **4** and **7** can be made on the basis of a 2D-^{13}C-nmr INADEQUATE spectrum. It allows the determination of the coupling constants of vicinal carbon atoms and provides, therefore, a connectivity pattern of the carbon skeleton. In structure (**7**) four carbon atoms form a cyclobutane ring, in **4** an oxygen atom interrupts the carbon chain. In order to carry out 2D-INADEQUATE measurements a choice has to be made with respect to the magnitude of the expected $^1J(CC)$ coupling constants. This permits the determination of the connectivity of carbon atoms with similar $^1J(CC)$ couplings. In our case we chose $^1J(CC) = 40$ Hz as reference which is typical for $^1J(CC)$ of sp^3-hybridized C-atoms.[6] The result of the experiment is that the methine C-atom at 107 ppm is bound to the methylene C-atom at 36 ppm which in turn is connected to a quarternary C-atom at 68 ppm. If these observations were to support structure (**7**) a cross signal would be expected for the signal at 107 ppm with a quarternary C-atom and another one for the signal at 68 ppm with the second quarternary C-atom. The absence of these signals excludes structure (**7**). Does it, however, support **4**? It is not expected to observe more than one $^1J(CC)$



Scheme 2

coupling for the signal at 107 ppm for **4**. A cross signal, however, is expected for the quarternary C-atom at 68.5 and 88.6 ppm. The fact, that it is not found, can be explained by the magnitude of $^1J(CC)$ coupling costants in three-membered rings, for instance cyclopropanes, which amounts to about 10 Hz. If this were also true for the oxirane ring no cross signal could have been observed because the experiment was calibrated to *ca.* 40 Hz.

In conclusion it can be stated that no other structure than **4** is in agreement with all the spectroscopic data. A simple rationalization for its formation can be given (Scheme 2). In a one-pot reaction a complicated bicyclic structure is generated which should be difficult to obtain by other means. It remains to be seen whether other polarized electron-rich double bonds will allow an extension of the synthetic scheme.

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EXPERIMENTAL

All reactions were carried out under argon in dry solvents. Melting points are uncorrected. Ir spectra were recorded on a Perkin-Elmer FT-IR 1600 spectrometer. ^{1}H-Nmr and ^{13}C-nmr spectra were obtained with Varian Gemini 200 and Bruker AMX 300 spectrometers (solvent $CDCl_3$, TMS as internal standard). Mass spectra were measured with a Finnigan MAT 312 or Fisons VG prospec 300 spectrometer.

2,3-Dihydro-2,2,3,3-tetraethoxy-5,6-dimethoxycarbonyldioxine (**2**): 0.35 g (2.0 mmol) of **1** and 0.41 g (2.0 mmol) of tetraethoxyethylene[7] were dissolved in 2.0 ml of dichloromethane. After 5 min at room temperature the yellow color of the diketone had disappeared. The solvent was removed in vacuo. 0.75 g of a colorless oil remained. A ^{1}H-nmr spectrum showed only one product, more than 95 % pure. The oil was chromatographed over alumina (neutral) with toluene / ethyl acetate 9:1, yield 0.68 g (90 %).

^{1}H-Nmr *(200 MHz)*: δ = 1.15 (t, ^3J=7.1 Hz, 12H, $-OCH_2C\underline{H}_3$), 3.74 (s, 6H, $-CO_2C\underline{H}_3$), 3.70 - 3.90 (m, 8H, $-OC\underline{H}_2CH_3$). ^{13}C-Nmr (50 MHz): δ = 15.2 ($-OCH_2\underline{C}H_3$), 52.5 ($-O\underline{C}H_2CH_3$), 59.7 ($-CO_2\underline{C}H_3$), 108.9 ($O-\underline{C}(OCH_2CH_3)_2$), 130.7 ($-\underline{C}=$), 162.2 ($-\underline{C}O_2CH_3$). Ir ($CHCl_3$): υ = 1735 (C=O), 1655 cm^{-1} (C=C). Ms (70 eV), *m/z* (%): 378 (0.1) [M^+], 333 (39) [$M-OC_2H_5^+$], 319 (12), 259 (70), 230 (45), 204 (51), 175 (88), 14 7(74), 119 (100), 91 (34), 47 (33), 29 (98). Anal. Calcd for $C_{16}H_{26}H_{10}$: C 50 79, H 6.93. Found C 50.63, H 6.96.

2,3-Dihydro-E-2,3-dimethoxy-5,6-dimethoxycarbonyldioxine (**3**): 0.23 g (1.3 mmol) of **1** and 0.12 g (1 3 mmol) of *E*-1,2-dimethoxyethylene[8] *were dissolved in* 2.0 *ml of dichloromethane* and stirred for 20 days at room temperature. The solvent was removed in vacuo. A ^{1}H-nmr-spectrum of the residue showed only one product in 60 % yield. Column chromatography over alumina (neutral) with toluene / ethyl acetate 1:1 gave 55% (0.18 g) of **3** as a colorless oil.

^{1}H-Nmr(300 MHz): δ = 3.52 (s, 6H, $-OC\underline{H}_3$), 3.82 (s, 6H, $-CO_2C\underline{H}_3$), 4.97 (s, 2H, $-C\underline{H}-$, $^3J_{H,H}$ = 1.0 Hz, (obtained from an indirect two-dimensional J-spectrum[9]). ^{13}C-Nmr (75 MHz) : δ = 52.6 ($-CO_2\underline{C}H_3$), 55.9 ($-O\underline{C}H_3$), 94.5 ($-\underline{C}H-$), 130.4 ($-\underline{C}=$), 162.5 ($-\underline{C}O_2CH_3$). Ir (film) υ = 1746 (C=O), 1651 cm^{-1} (C=C). Ms (70 eV), *m/z*(%): 262 (4) [M^+], 88 (100), 83 (71), 73 (26), 59 (18), 45 (28). $C_{10}H_{14}O_8$ Calcd. 262.0689, found 262.0656.

4,5-Dihydro-2,3-dimethoxycarbonyl-2,3-epoxy-5-ethoxyfuran (**4**): 0.35 g (2.0 mmol) of **1** and 0.14 g (2.0 mmol) of ethyl vinyl ether were dissolved in 2.0 ml of dichloromethane and the reaction mixture was stirred for 24 h at room temperature. After removal of the solvent in vacuo *0.48 g of a colorless, oil was obtained.* A *^{1}H-nmr-spectrum* showed one main product, *ca.* 90 % pure. This product was isolated by column chromatography on alumina (neutral, ethyl acetate / pyridine 99:1), yield 0.41 g (85 %). The oil crystallized from ethyl acetate / pentane 1:1 at -30 °C, mp 58 °C.

^{1}H-Nmr(200 MHz): δ = 1.25 (t, ^3J=7.2 Hz, 3H, $-OCH_2C\underline{H}_3$), 2.48 (dd, ^3J=1.8 Hz, ^2J=14.9 Hz, 1H, 4-H), 3.08 (dd, ^3J=6.9 Hz, ^2J=14.9 Hz, 1H, 4-H'), 3.52 (dq, ^3J=7,2 Hz, ^2J=9.6 Hz, 1H, $-OC\underline{H}_2CH_3$), 3.94 (dq, ^3J=7.2 Hz, ^2J=9.6 Hz, 1H, $-OC\underline{H}_2CH_3$), 3.87 (s, 3H, $-CO_2C\underline{H}_3$), 3.91 (s, 3H, $-CO_2C\underline{H}_3$), 5.68 (dd, ^3J=1.8 Hz, ^3J=6.9 Hz, 1H, 5-H). ^{13}C-Nmr(75 MHz): δ = 14.9 ($-OCH_2\underline{C}H_3$), 36.3 ($-\underline{C}H_2-$), 53.5, 54.1 ($-CO_2\underline{C}H_3$), 65.2 ($-O\underline{C}H_2CH_3$), 68.5, 88.6 (oxirane-C), 107.1 ($-\underline{C}H-OCH_2CH_3$), 162.7, 164.7 (-C$O_2CH_3$). Ir ($CHCl_3$): υ = 1763, 1740 cm^{-1} (C=O). Ms (70 eV), *m/z* (%): 246 (0.1) [M^+], 229 (0.5) [$M-OH^+$], 214 (4), 187 (4) [$M-CO_2CH_3^+$], 159 (46), 113 (21), 99 (100), 84 (17), 71 (58), 59 (57), 49 (19), 43 (34), 29 (19), 15 (59). Anal. Calcd for $C_{10}H_{14}O_7$: C 48.78, H 5.73. Found C 48.71, H 5.82.

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