Singlet-Oxygen Photolysis of Dihaloketones. A Facile and Efficient Approach to Vicinal Triketones and Their Monohydrates

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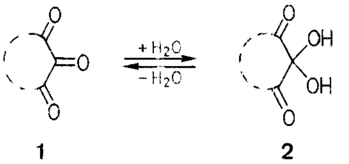
The preparation of *vic*-triketones and/or their monohydrates by sensitized photooxidation (singlet oxygen) of *gem*-dihaloketones and/or *vic*-dihaloketones is described; some reaction mechanisms are discussed.

Vicinal triketones **1** and their monohydrates **2** have received remarkable interest by virtue of their wide applications for analytical and synthetic purposes.[1] Thus, they are used for the quantitative analysis of amino acids (Strecker degradation[2]) as well as for the detection of peptides, proteins, primary amines, and ammonia, particularly, in biological fluids.[1b,3]



1 **2**

Scheme **A**

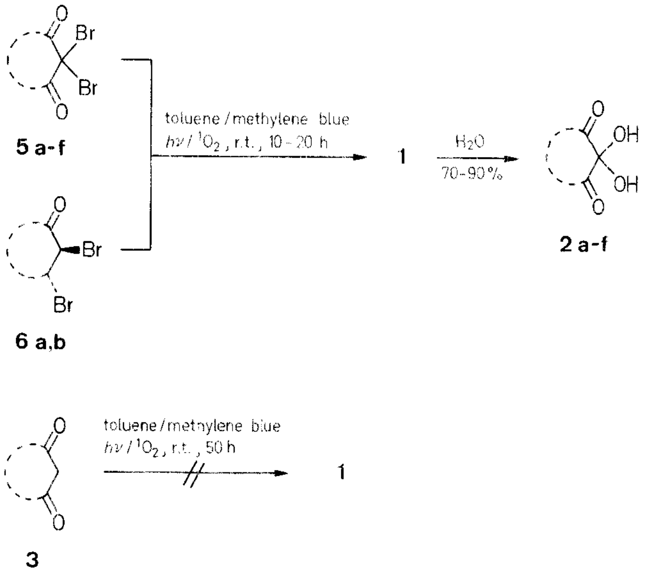
The methods described so far for the synthesis of triones **1**, e.g., by halogenation and hydrolysis of 1,3-diketones,[4] by cleavage of aminals with diluted acids,[5a,6] by oxygen-halogen insertion in 2-diazo-1,3-dioxo compounds,[7] by ozonolysis of iodonium and/or sulfonium ylides,[8] and with the halogen-dimethyl sulfoxide system as oxidizing agent[9] are of special but limited use. A general procedure utilizing some of these methods for the synthesis of rather different polycarbonyl compounds in high yield, such as 1,2,3-indanetrione (**1a/2a**), quinoline-2,3,4-trione (**1b, c/2b, c**), 2,3-dihydrophenalene-1,2,3-trione (**1d/2d**), or 1,3-diphenylpropanetrione (**1e, f/2e, f**) (cf. Scheme **B**), is hitherto not available.

Our interest in the chemistry of *vic*-triketones and their monohydrates[10,11] made us develop an efficient and simple approach to the synthesis of compounds **1** and/or **2**. This general method consists of the photosensitized oxidation of *gem*-2,2-dihalo-1,3-diketones (**5**) and/or α,β-dihaloketones (**6**) and affords the title compounds directly and in high yield.

Thus, singlet-oxygen photolysis of a 1% solution of the *gem*-dihalides **5** in toluene for 15 h using a pyrex filter (~280 nm) with methylene blue as sensitizer results in the formation of the triones **1** in 80–90% yield. Due to the high electrophilicity of the midstanding carbonyl group[1a,8a] in **1**, these compounds are isolated as hydrates **2** due to solvatation by water which is unavoidably present in the reaction medium during handling.

Without circulation of oxygen, the photolysis of 2,2-dibromo-1,3-diketones **5** also gave products **2**, but in lower yield (~60–70%) and after longer irradiation times (40–60 h). However, when oxygen was circulated through the toluene solution in the dark for ~15 h, compounds **5** were recovered practically unchanged, even after addition of traces of water to the reaction mixture.

The identity of products **2** was established by comparison of the m.p.s and IR spectra with those of authentic samples. The monohydrates **2e, f** were obtained accordingly in ~75% yield by sensitized photooxidation of the appropriate α,β-dibromoketones **6a, b** (Scheme **B**).

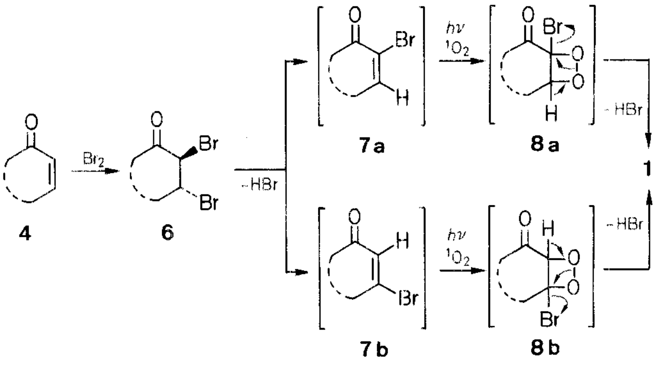


Scheme **B**

Singlet oxygen has occasionally been used for the introduction of vicinal carbonyl groups. Thus, α-enamine ketones react with singlet oxygen to give the corresponding α-diketones in high yield.[12] In another approach, the fluoride-promoted, dye-sensitized photooxidation of enoles, *via* an "ene"-type reaction, followed by dehydratation affords tricarbonyl compounds which spontaneously undergo hydration.[13]

Recently, a process was reported[14] in which cyclic vicinal tetraketones are generated by oxidation of dihydroxydiketones or hydroxytriketones with *N*-bromosuccinimide or nitric acid.

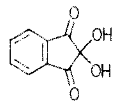
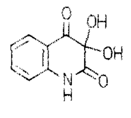
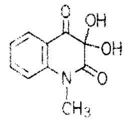
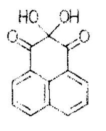
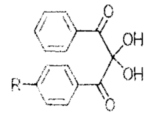
The formation of the triones **1**/monohydrates **2** by singlet-oxygen photolysis of α,β-dihaloketones (cf. Scheme **C**) can be rationalized by assuming initial elimination of hydrogen bromide (identified as triethylamine hydrobromide) to give unsaturated monobromo species such as **7a, b** which undergo [2+2]-cycloaddition with singlet oxygen[15] to give the elusive 1,2-dioxetanes **8a, b**. Elimination of hydrogen bromide and metathetic ring cleavage[16] then produces triketones **1**. The direct photo-induced oxidation of the 1,3-diones **3a–f** with singlet oxygen to give triones **1** was not successful, however.

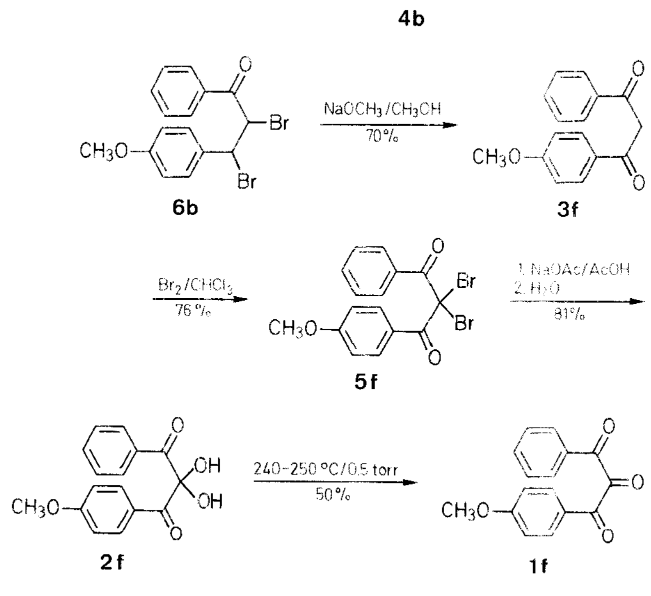


Scheme **C**

Compounds **2f** and **1f** were prepared by the following sequence, using in part the procedure of Lit.[4c]

Table. Vicinal Triketone Monohydrates **2** Prepared

Educt	Irradiation Time (h)	Photooxidation Product (Hydrates)	Yield (%)	m.p. (%)	Molecular Formula or Lit. m.p. (°C)
5a	12	 **2a**	80	120–130	125–130[5b]
5b	15	 **2b**	87	120–170	120–170[6]
5c	15	 **2c**	90	110–120	110–120[5a]
5d	10	 **2d**	83	265–270	267–270[4b]
5e	10	 **2e** R = H **2f** R = OCH$_3$	90	60–70	60–70[4c]
5f	10		85	130–165	$C_{16}H_{14}O_4$ (270.3)
6a	20	**2e**	70	60–70	60–70[4c]
6b	20	**2f**	70	130–165	$C_{16}H_{14}O_4$ (270.3)



Melting points are uncorrected; IR spectra: Perkin-Elmer 197 (in KBr). Authentic specimens of *vic*-triketones **1a–f** and their monohydrates **2a–f** were prepared according to known procedures.[4–8,17,18]

The irradiation experiments are carried out in a pyrex reactor (λ ~ 280 nm) equipped with a high-pressure mercury lamp (Philips HPK 125).

Singlet-Oxygen Photolysis of Dihaloketones 5a–f and 6a, b; General Procedure:

A solution of the dihaloketones **5a–f** or **6a, b** (2.5 g, 8 mmol) in toluene (250 ml) containing methylene blue (30 mg) is irradiated while oxygen is circulated through the solution at a moderate rate. The reaction is monitored by TLC. After disappearance of the starting material (irradiation time, see Table), the solvent is removed *in vacuo*, and the residue recrystallized from an appropriate solvent in the presence of Norite (to remove traces of sensitizer). Due to the sensitivity of the resultant triketones **1a–f** under the work-up conditions (some water is present in the mixture), the monohydrates **2a–f** are obtained instead of the free ketones.

Photolysis of Compounds 5a–f without Circulating Oxygen; Typical Procedure:

A solution of compound **5a** (2.5 g) in toluene (250 ml) is irradiated and the progress of the reaction is monitored by TLC. After disappearance of **5a** (~ 40 h), the solvent is removed *in vacuo* and the residue crystallized from water to give colorless crystals of product **2a**; yield: 0.87 g (60 %). In a similar manner, compounds **5b–f** are converted into the monohydrates **2b–f**.

Dark Experiments; General Procedure:

Oxygen is bubbled into a solution of a compound **5a–f** (0.5 g) in toluene (50 ml) containing traces of water (1 ml). After 15 h, the volatile components are removed *in vacuo* and the residue is recrystallized from a suitable solvent. The product proves to be unchanged starting material (m.p., mixture m.p., and comparison of IR spectra).

Singlet-Oxygen Photolysis of the 1,3-Diones 3; Typical Procedure:

A solution of dibenzoylmethane **3e** (2.5 g) in toluene (250 ml) containing methylene blue (30 mg) is irradiated while oxygen is circulated through the solution at a moderate rate. After 50 h, the solution is evaporated to dryness, and the residue recrystallized from light petroleum (b.p. 40–60 °C) to give colorless needles. The product (2.2 g, 90 %) proves to be unchanged **3e** (m.p. and mixture m.p. 77–78 °C[5e]).

1-(4-Methoxyphenyl)-3-phenylpropanetrione (1f):

1-(4-Methoxyphenyl)-3-phenylpropen-3-one **(4b)**: Acetophenone (52 g, 0.43 mol) and 4-methoxybenzaldehyde (61.2 g, 0.45 mol) are reacted in aqueous 18% sodium hydroxide (120 ml). The product is isolated by suction and recrystallized from ethanol; yield: 82.4 g (80 %); colorless crystals, m.p. 75–77 °C.

$C_{16}H_{14}O_2$	calc.	C 80.62	H 5.93
(238.1)	found	80.25	5.87

MS (70 eV): $m/e = 238$ (M^+).

IR (KBr) $\nu = 1725$ (CO); 1640 (C=C) cm^{-1}.

1,2-Dibromo-1-(4-methoxyphenyl)-3-phenylpropan-3-one **(6b)**: Bromine (50.4 g, 0.31 mol) is added to a stirred solution of compound **4b** (75 g, 0.31 mol) in tetrachloromethane (200 ml). Product **6b** is isolated by suction and recrystallized from ethanol to give pale yellow crystals; yield: 90.3 g (72 %); m.p. 180 °C.

$C_{16}H_{14}Br_2O_2$	calc.	C 48.25	H 3.54	Br 40.16
(396.9)	found	48.57	3.32	39.26

MS (70 eV): $m/e = 397$ (M^+).

IR (KBr): $\nu = 1745$ (C=O); 740 (C–Br) cm^{-1}

1-(4-Methoxyphenyl)-3-phenylpropane-1,3-dione **(3f)**: To a solution of compound **6b** (85 g, 0.21 mol) in ethanol (200 ml) sodium methoxide (54 g, 0.46 mol) is added slowly and the resultant mixture refluxed for 15 h. Product **3f** is isolated by suction and recrystallized from ethanol to give colorless needles; yield: 37.8 g (70 %); m.p. 98 °C.

$C_{16}H_{14}O_3$	calc.	C 75.56	H 5.55
(254.1)	found	75.47	5.13

MS (70 eV): $m/e = 254$ (M^+).

IR (KBr): $\nu = 1740$ (C=O) cm^{-1}

2,2-Dibromo-1-(4-methoxyphenyl)-3-phenylpropane-1,3-dione **(5f)**: To a stirred solution of compound **3f** (35 g, 0.13 mol) in chloroform (20 ml), a solution of bromine (44.8 g, 0.28 mol) in chloroform (100 ml) is added dropwise, with ice cooling, over a period of 30 min. The yellow crystalline product **5f** is isolated by suction and recrystallized from ethanol; yield: 43.1 g (76%); m.p. 122°C.

$C_{16}H_{12}Br_2O_3$	calc.	C 46.61	H 2.94	Br 38.79
(411.9)	found	45.84	2.70	38.36

MS (70 eV): $m/e = 411$ (M^+).

IR (KBr): $\nu = 1750$ (CO); 735 (C–Br) cm^{-1}.

1-(4-Methoxyphenyl)-3-phenylpropanetrione Monohydrate (**2f**):[4c] A solution of (fused) sodium acetate (18.8 g, 0.23 mol) in hot glacial acetic acid (80 ml) is prepared in a 500 ml round-bottomed flask, compound **5f** (50.6 g, 0.12 mol) is added, and the mixture is heated to boiling until the precipitation of sodium bromide ceases (1.5–2 h). The mixture is then cooled to room temperature, water (120 ml) is added to dissolve the precipitated salt and to precipitate product **2f** as a white substance which is isolated by suction; yield: 28.5 g (81%); m.p. 130–165°C.

$C_{16}H_{14}O_5$	calc.	C 67.11	H 4.93
(286.3)	found	66.58	4.72

IR (KBr): $\nu = 3400$ (OH); 1750, 1720 (CO) cm^{-1}.

1-(4-Methoxyphenyl)-3-phenylpropanetrione (**1f**): Compound **2f** (25 g, 80 mol) is distilled at 0.5 torr at a bath temperature of 240–250°C. Product **1f** is obtained as an oil which solidifies to give pale yellow crystals; yield: 11.7 g (50%); m.p. 168–170°C.

$C_{16}H_{14}O_4$	calc.	C 71.67	H 4.51
(268.1)	found	71.18	4.37

MS (70 eV): $m/e = 268$ (M^+).

IR (KBr): $\nu = 1765$, 1730 (CO) cm^{-1}.

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In memory of Professor Dr. Alexander Schönberg.

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