

On the Chemistry of Stable α -Oxoketenes

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This short review describes the preparation and chemistry of sterically stabilized α -oxoketenes, which can be isolated and handled as true neat compounds. Their reactions with dienophiles afford [4+2] – as well as [2+2] cycloadducts depending on their ability to adopt that conformation suitable for each type of cycloaddition reactions. Addition of nucleophiles leads either to dipivaloylacetic acid derivatives as expected products or to the rare molecular skeleton of mono- or bifunctionalized bridged bisdioxines, which exhibit axial chirality. The bifunctionalized derivatives may serve as novel spacer units in several macrocyclic systems.

Key words: α -oxoketenes, preparation and chemistry, cycloaddition reactions, addition of nucleophiles, bridged bisdioxines, macrocycles.

INTRODUCTION

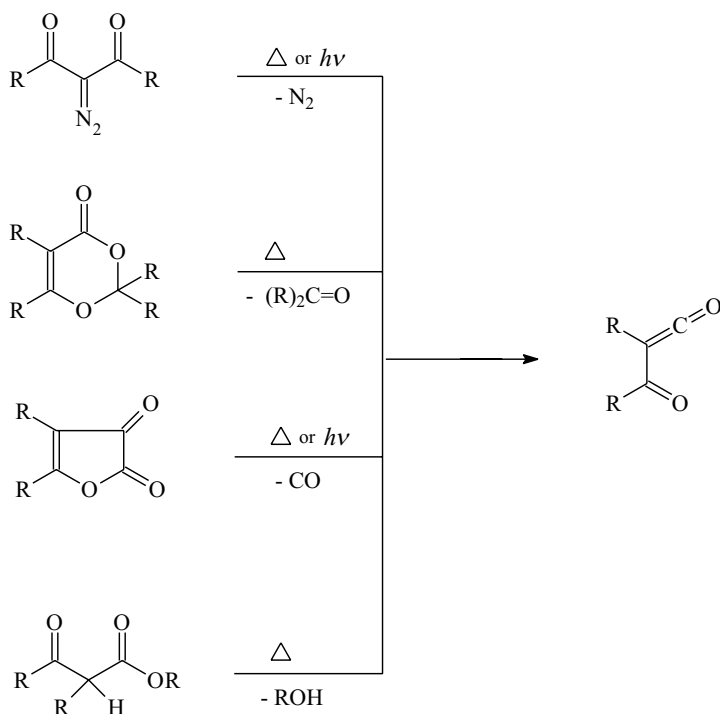
α -Oxoketenes¹ in general are usually highly reactive molecules, which normally cannot be isolated or observed under ordinary reaction conditions. However, they can be stabilized both sterically and electronically, and ketene carboxylic acid derivatives in particular are extraordinarily stable.^{2–6} This article focuses on neat α -oxoketenes only, which are sterically stabili-

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zed and may be handled at room temperature and under normal pressure. Ketene carboxylic acid derivatives²⁻⁶ as well as fluorinated compounds⁷ will be excluded.

PREPARATION

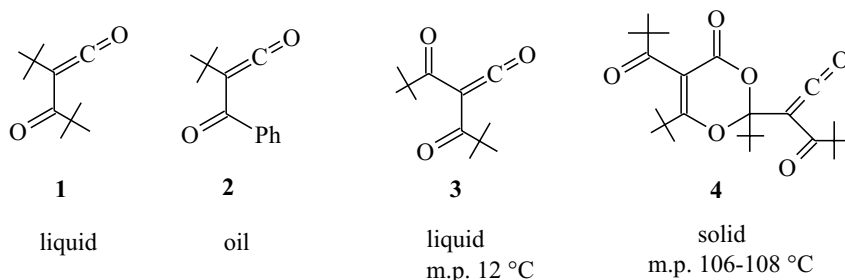
Synthetic useful procedures for the generation and/or preparation of α -oxoketenes in general include thermolysis and photolysis of 2-diazo-1,3-dicarbonyl compounds,^{8,9} solution thermolysis or photolysis of 1,3-dioxinones^{10,11} and thermolysis of furan-2,3-diones,¹² β -keto-esters¹³ and acid chlorides¹⁴ (see Scheme 1).



Scheme 1

Most of the α -oxoketenes generated by these pathways are observed and characterized at very low temperatures in Ar-matrices,¹ some of them exist in inert solutions^{1,15,16} but very few can in fact be isolated as neat compounds at room temperature. In particular, the bulky *tert*-butyl group obviously plays an important role in stabilizing the ketene moiety dramatically.

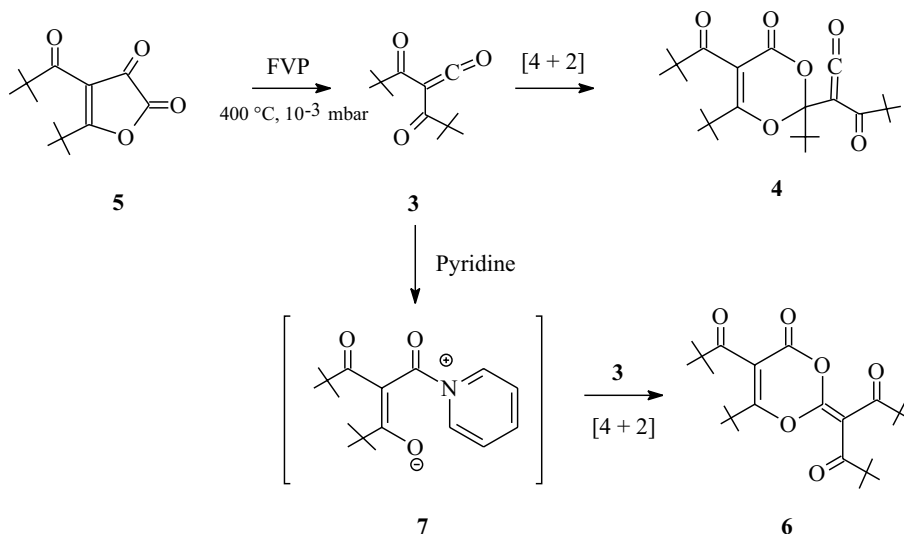
Browsing through the literature of α -oxoketenes only three compounds were so far described to be obtainable as *neat* compounds : *tert*-butyl-pivaloylketene (**1**),^{17,18} benzoyl-*tert*-butylketene (**2**),¹⁹ dipivaloylketene (**3**)²⁰ and its dimer, 2-[3,3-dimethyl-2-oxo-1-(oxomethylene)butyl]-2,6-di-*tert*-butyl-5-pivaloyl-1,3-dioxin-4(2*H*)-one (**4**)²⁰ (Scheme 2) :



Scheme 2

Oxoketene **1** has been prepared *via* two different routes, namely photolysis of the corresponding diazodiketon in dimethylsulfide (53% yield)¹⁸ or from reaction of *tert*-butylmalonyl chloride and an excess of $\text{Bu}_2(\text{CuCN})\text{Li}_2$ (33% yield) after purification by preparative GC.¹⁷ The absorption band of the ketene-moiety in the IR(CCl_4) is detected at 2100 cm^{-1} (vs).^{17,18} Compound **2** was obtained as a by-product during synthesis of ynolesters¹⁹ and properly characterized by IR (neat, 2103 cm^{-1}) as well as HRMS, ^1H and ^{13}C NMR spectra. However, the chemistry of **1** and **2** has not been explored further so far.

In contrast, α -oxoketene **3** has been generated in excellent yields (90–95%) from flash vacuum pyrolysis ($400\text{ }^\circ\text{C}$, 10^{-3} mbar) of *tert*-butyl-pivaloylfuran-2,3-dione (**5**) and was fully characterized spectroscopically (*e.g.* IR(KBr): 2119 cm^{-1}).²⁰ At room temperature it slowly dimerizes in an unusual [4+2] cycloaddition reaction to the dioxinone **4**, which, although still an α -oxoketene, is extraordinarily stable (see Scheme 2), its ketene absorption band (IR, KBr pellet) is found at 2115 cm^{-1} . When the dimerization is carried out in the presence of DMSO or pyridine, a different dimer **6** is formed, probably *via* a zwitterionic intermediate, *e.g.* **7** (Scheme 3).²¹ A surprisingly stable representative composed from **3** and 4-dimethylaminopyridine has been described quite recently.²² Both dimers are obtained in excellent yields (88%, 96%, respectively). Semiempirical AM1 calculations reveal somewhat lower activation energies for cycloaddition reactions of dipivaloylketene across its C=O double bond leading to **4** and **6**, respectively, compared to the usual C=C addition product.²³



Scheme 3

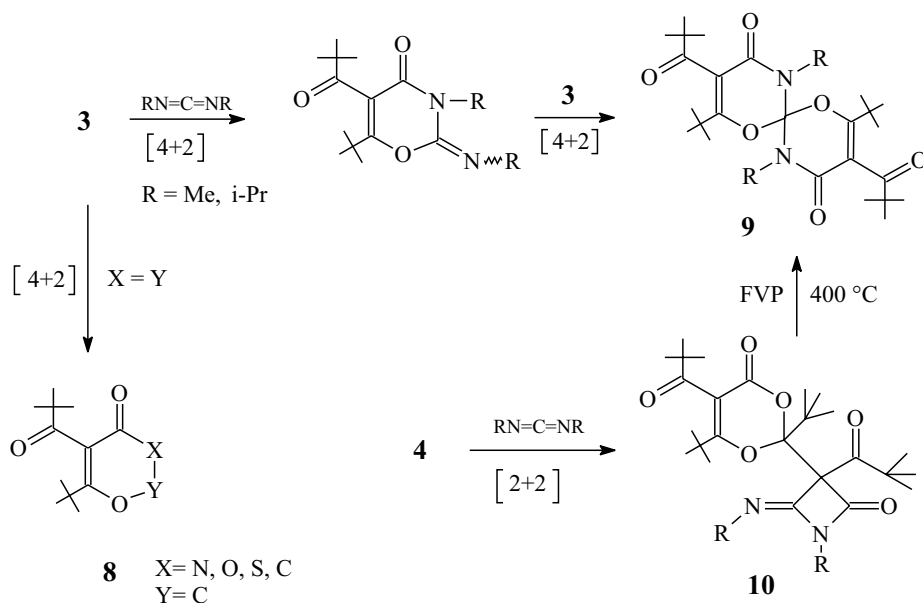
CHEMISTRY

Ketenes in general and α -oxoketenes in particular are known to undergo two main types of reactions : A) Cycloaddition reactions;

B) Addition of nucleophiles.

A) *Cycloaddition reactions* : It is text-book chemistry that ketenes usually add to multiple bond systems *via* a [2+2] process across their C=C as well as C=O double bonds, while α -oxoketenes show a pronounced tendency to form [4+2] hetero-Diels Alder adducts when trapped with dienophiles. In fact, dipivaloylketene (**3**) adds various polarized multiple bond systems to form the expected [4+2] adducts **8** in high yields at very mild reaction conditions.^{21,24} Surprisingly, employing alkyl-carbodiimides as dienophiles 2:1 adducts **9** could be obtained. The chirality of these dissymmetric molecules was established by ¹H NMR studies applying chiral shift reagents (Scheme 4).²¹ Compared to dipivaloylketene (**3**) the dimeric oxoketene **4** was rather reluctant to undergo cycloaddition reactions with dienophiles: Only in case of alkylcarbodiimides again 1:1 adducts could be isolated in good yields (58%; 76%, respectively). Instead of the expected [4+2] adduct, however, these substances were shown to be [2+2] cycloadducts **10**, a final structural confirmation came from an X-ray crystallographic analysis.²¹ Compared to the vast number of papers dealing with [4+2] adducts derived from α -oxoketenes reports on [2+2] cycloadditions to acylketenes are extremely rare.²⁵ The ten-

gency of **4** to form [2+2] rather than [4+2] adducts can be ascribed to the highly hindered ketene functionality, in particular to the fact, that the α -oxoketene moiety has *s-E* conformation as established by X-ray crystallography²⁰ and obviously too has difficulties to adopt the *s-Z* conformation in solution. These findings were also supported by *ab initio* – and semi-empirical calculations indicating a rotational barrier *s-E* / *s-Z* of approximately 15 kcal mol⁻¹.²⁶ Attempts to selectively cleave the dioxinone ring in **10** to generate the simple imino-azetinone derivative failed. Instead, when **10** was subjected to FVP again the spiro-compound **9** was isolated in 84% yield as a result of a complete cycloreversion of both rings to **3** and the carbodiimide and subsequent 2-fold [4+2] addition of dipivaloylketene (**3**) to the carbodiimide (Scheme 4).



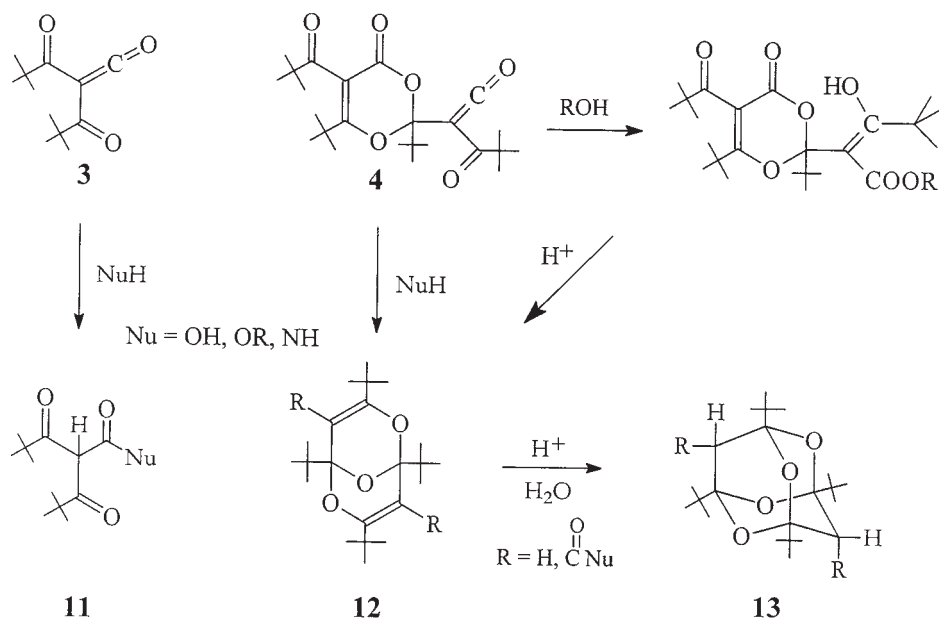
Scheme 4

B) *Addition of nucleophiles* : Reaction of the monomeric dipivaloylketene (**3**) with nucleophiles provides the corresponding dipivaloyl acetic acid derivatives **11** in excellent yields^{20,27,28} thus following the usual behaviour of ketenes in general.²⁹ Remarkably, derivatives **11** do not show any tendency to enolize in solution, they exist as tricarbonyl species demonstrated by the C-H signals in the NMR spectra (¹H : δ 5.8–6.8 ppm, ¹³C : δ 60–65 ppm).^{28,30,31} Dipivaloyl acetic acid amides or –thioesters were obtained also from reaction of the dimeric oxoketene **4** with aliphatic amines or thiolates (the latter in

the presence of triethylamine), offered in a molar ratio of 1 : 2, thus indicating a re-splitting of the dioxinone ring of **4** after primary addition of the nucleophile to the ketene moiety.²⁷

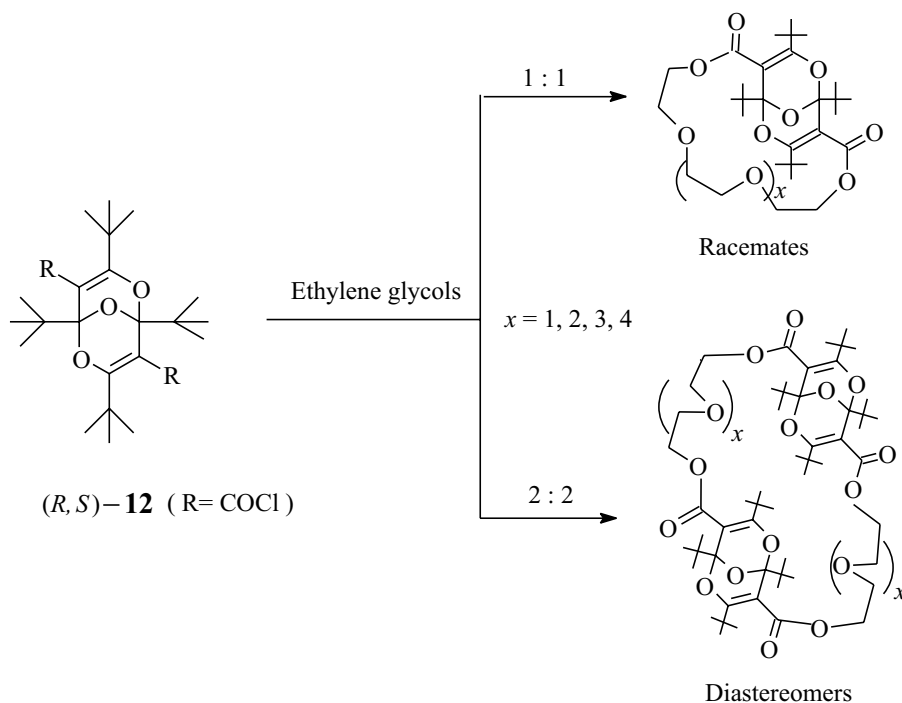
However, when oxoketene **3** was reacted with primary aromatic amines at room temperature in methylene chloride, spontaneous decarboxylation occurred, and trioxabicyclononadienes (»bridged bisdioxines«) **12**, having one carboxylic acid amide side chain were isolated in high yields. These molecules represent the rather rare molecular skeleton of a concave, bridged bisdioxine ring system exhibiting axial chirality.^{27,32} In addition to spectroscopic data, their structure was confirmed by an X-ray analysis.³² A similar picture was found from reaction of **4** with OH-nucleophiles.²⁷ Here the primary adduct of the corresponding nucleophile to the ketene moiety could be isolated and characterized and further transferred by acidic catalysis into the bridged bisdioxine system, now having two carboxylic acid functionalities (Scheme 5).²⁷ The spontaneous formation of this bridged bisdioxine skeleton in those reactions is likely to proceed *via* an unusual [4+4] tandem cyclization reaction. This mechanistic pathway was also supported by semiempirical molecular orbital calculations.²⁷

Furthermore, the bicyclic dioxines **12** can easily be converted by acidic hydrolysis into functionalized 2,4,6,8-tetraoxadamantanes **13**, again a very



Scheme 5

rare molecular scaffold which also exhibits axial chirality, established by ^1H NMR studies using $\text{Eu}(\text{hfc})_3$ as chiral shift reagents.^{33,34}



Scheme 6

Due to their concavity and chirality the bifunctionalized bisdioxines **12** were expected to serve as novel spacer groups in several macrocyclic systems which might further apply as potential host-molecules within the area of host-guest chemistry. Preliminary examples of such ring systems of different size are presented in Scheme 6.

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SAŽETAK**O kemiji stabilnih α -oksoketena**

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Opisana je priprava i kemija sterički stabiliziranih α -oksoketena. Njihove reakcije s dienofilima daju [4+2] i [2+2] cikloadukte, ovisno o sposobnosti stvaranja prikladnih konformacija. Adicija nukleofila daje derivate ditrimetilacetiloctene kiseline ili neke vrlo rijetke molekulske strukture mono- i difunkcionaliziranih premoštenih bisdioksina, koji pokazuju aksijalnu kiralnost. Difunkcijski derivati mogu poslužiti kao nove razmaknice (space units) u makrocikličkim sustavima.