THE CHEMISTRY OF 1,4-DIOXENE (2,3-DIHYDRO-1,4-DIOXIN) . PART VIII[1]†

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Abstract - The chemistry of 1,4-dioxene has been reviewed, with a special emphasis on reactions potentially useful in synthesis .

INTRODUCTION

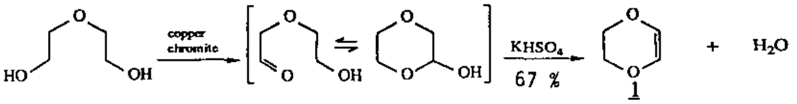
Although dioxene 1 *(2,3-dihydro-1,4-dioxin) has been known for many years*[2], its chemistry and application to synthesis have been explored only in rare occasions .

Dioxene is a colourless liquid (b p : 94°C), sparingly soluble in water, which can be stored in a refrigerator without any alteration for at least one year . Its half-chair conformation has been established by nmr[3], and confirmed by analysis of its ir and Raman spectra, as well as by molecular mechanics calculations[4] .

Its first ionization potential (I.P.) (8.43 eV) has been determined by photoelectron spectroscopy. It is slightly lower than the corresponding I.P. of dihydropyran (8.84 eV) in agreement with ab initio calculations[5] .

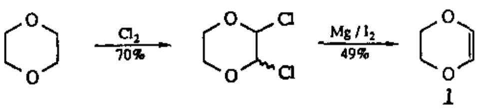
PREPARATION

It is extremely easy to prepare large quantities of dioxene from diethylene glycol (copper *chromite* - $KHSO_4$, 230°C) *on the basis of the following reaction* :

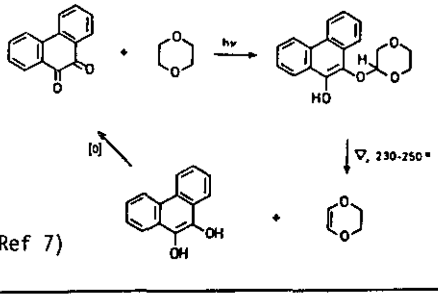


A mixture of dioxene and water distills off . Due to its poor solubility in water, dioxene can easily be separated and dried up[6] .

Two other methods, which are not amenable to large scale production, have been published[2,7] .



(Ref 2)



(Ref 7)

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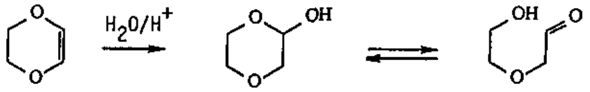
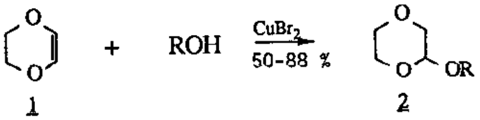
† *Dedicated to Professor D.H.R. Barton on the occasion of his 70th birthday .*

ADDITION REACTIONS

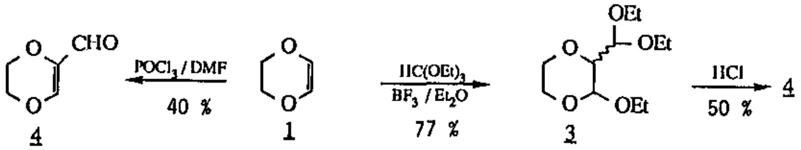
Like any enol ether, dioxene undergoes very easily addition reactions in the presence of acids. Dioxene is readily hydrolysed with acidified water, being converted into 2-hydroxydioxan, which is in equilibrium with 5-hydroxy-3-oxapentanal[8] :



Alcohols add to dioxene in the presence of cupric bromide[9] (rather than p-toluenesulphonic acid) to form 1,4-dioxan-2-yl ethers :

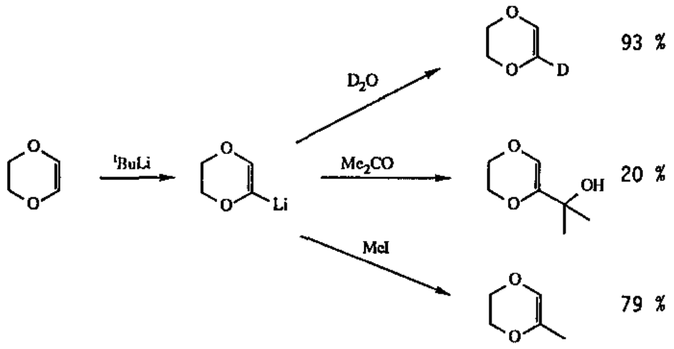


The protected alcohol 2 can be regenerated in good yield (HCl/water). Reactions of dioxene with halogens proceed smoothly affording 2,3-dihalogenodioxans[10]. Triethyl orthoformate reacts smoothly with dioxene in the presence of BF_3/Et_2O. The addition compound 3 which can be distilled, yields 2-formyldioxene 4 under mild conditions[11].
The same aldehyde 4 could be obtained in moderate yield by a Vilsmeier reaction[12] :



It has been shown by Saylor and Sebastian[13] that dioxene can readily be lithiated (t-butyllithium in THF at low temperature). They carried out some reactions with this new intermediate (Scheme 1).

Scheme 1



The scope of this scheme may easily be widened by combining the simple reaction of 2-dioxenyllithium with the specific properties of the dioxene ring. In fact, starting from a ketone or an aldehyde, it is possible to graft a chain containing one or two carbon atoms with oxygenated functionalities (Chart 1).

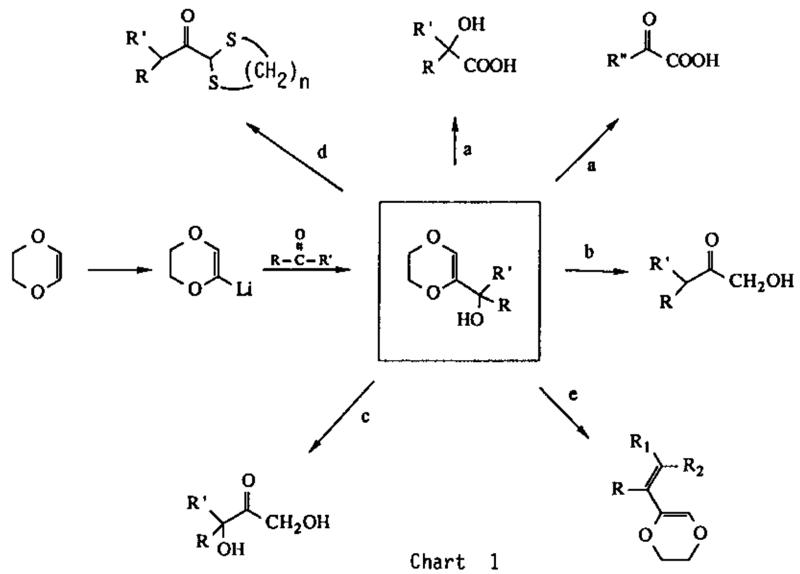
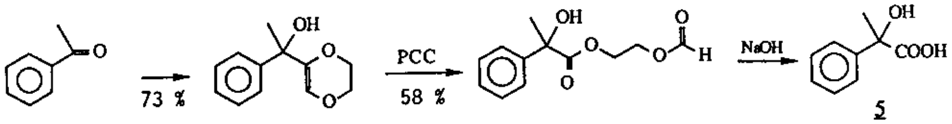


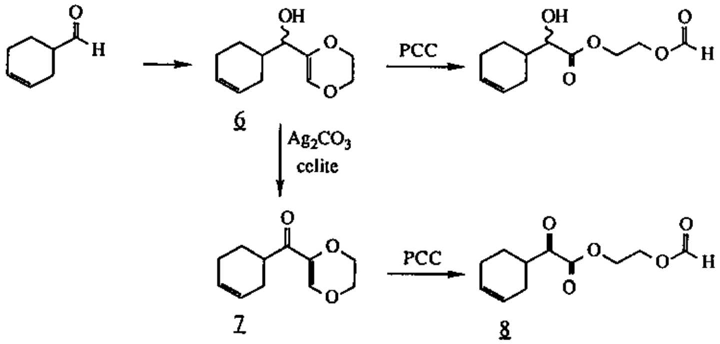
Chart 1

(a) Synthesis of α-hydroxy and α-keto acids [1]

The dioxene ring is very rapidly cleaved by pyridinium chlorochromate (PCC) . Thus (±)-atrolactic acid 5 was obtained from acetophenone by this procedure in a better overall yield than through the well established cyanohydrin method[14] :



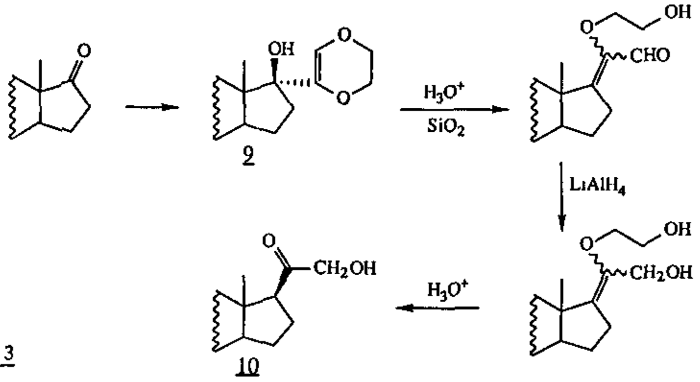
Oxidation of the dioxene moiety is so fast that even a secondary alcohol such as 6 remains virtually unaffected . However, ketone 7 could also be oxidized, albeit much more slowly than the corresponding secondary alcohol, into a α-keto acid derivative 8[1] (Scheme 2) .



Scheme 2

(b) Synthesis of α-hydroxymethyl ketones [15]

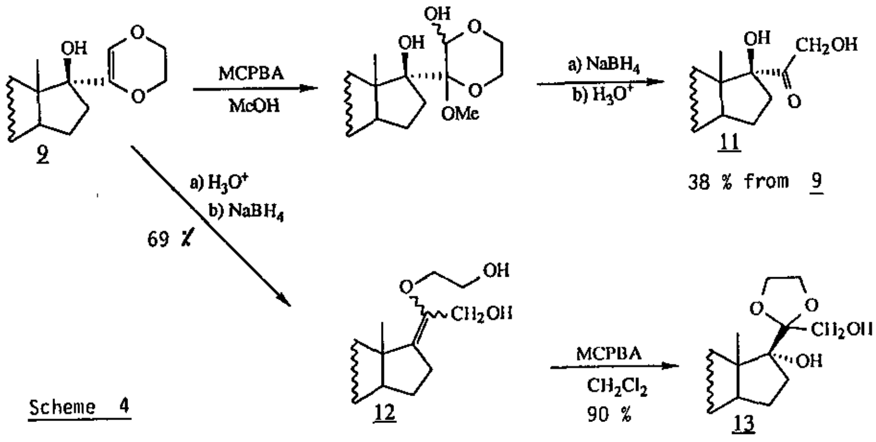
The tertiary alcohol 9 obtained from 17-ketosteroids and dioxenyllithium undergoes an allylic rearrangement under very mild conditions (silica gel - 5 % oxalic acid ; room temperature) . Reduction ($LiAlH_4$) of the resulting compound, followed by acid hydrolysis of the enol ether, affords the hydroxymethyl ketone 10 in 40 % overall yield (Scheme 3) .



Scheme 3

(c) Synthesis of α,α'-dihydroxy ketones [16]

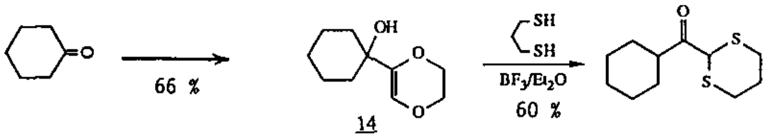
The intermediate 9 of the latter reaction sequence can be oxidized by m-chloroperbenzoic acid (MCPBA) in methanol . Sodium borohydride reduction and acid hydrolysis leads to α,α'-dihydroxy ketone 11 . In the steroid series, the side chain has the 17α (non natural) configuration. However, epoxydation in dichloromethane of the intermediate 12 with MCPBA gives directly the ethylene ketal of 17α,21-dihydroxy-20 keto compounds 13[17] (Scheme 4) .



Scheme 4

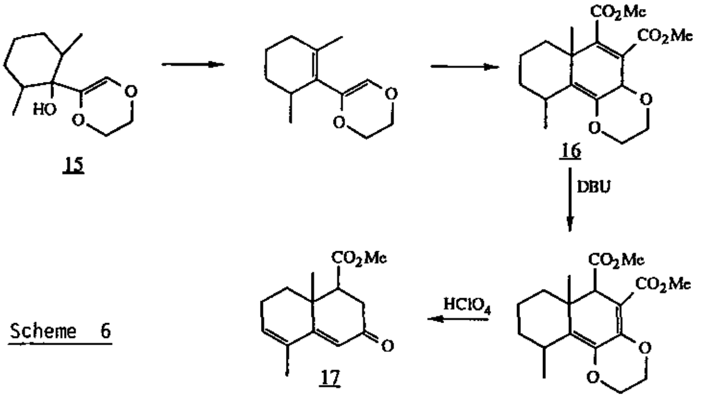
(d) Synthesis of α-keto thioketals [18]

1,4-Dioxenyl carbinols, such as 14 react with 1,3-propanedithiol in the presence of boron trifluoride, and lead to α-ketopropylene thioketals .



(e) Functionalized conjugated dienes [19]

Dehydration of tertiary alcohols of type 15 can be achieved without allylic rearrangement by using MsCl-Et$_3$N or SOCl$_2$-Py . The resulting functionalized dienes undergo [4 + 2] cycloaddition with various dienophiles . Thus, exposure of 16 obtained by Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD) to DBU followed by acidic hydrolysis afforded the highly functionalized compound 17 (Scheme 6) . Wittig reaction on 2-formyldioxene 4 gives similar dienes[20] .



Scheme 6

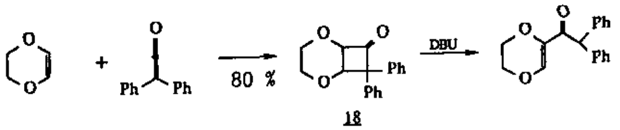
(f) Miscelaneous reactions

Some Fischer-type carbenes have been prepared from dioxenyllithium and chromium hexacarbonyl . They react normally with acetylenes to give substituted benzoquinones[21] .

CYCLOADDITIONS

Dioxene reacts with olefins upon uv irradiation and affords substituted dioxanes (Chart 2) . However, since dioxanes are very resistant to hydrolysis, these compounds have so far no application in synthesis[22-26] .

Paterno-Büchi cycloaddition of dioxene to carbonyl compounds yields the expected compounds but these adducts have not been examined further yet[27-29] .
Cycloaddition of diphenylketene to dioxene has been described[30a] . Its kinetic has also been studied[30b] . The resulting cyclobutanone 18 is almost quantitatively transformed to a new dioxenyl ketone by heating with DBU[17] :



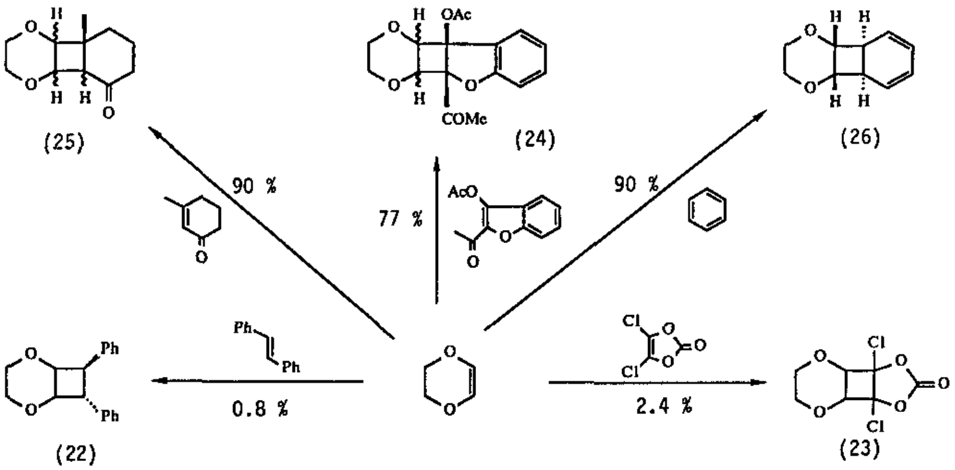
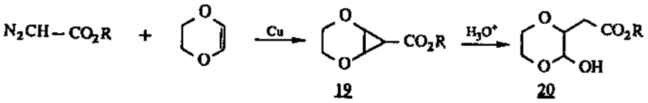


Chart 2

A [2 + 2] cycloaddition of $^1O_2$ to dioxene gives a dioxetane, which is thermally decomposed into ethylene glycol diformate[31] . A photochemical [2 + 3] cycloaddition has been mentioned[32] . Carbenes also react as expected to give cyclopropanes . For instance, ethyl diazoacetate decomposes in the presence of finely divided copper and dioxene to give 19 which upon acidid treatement affords 20[33] :



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