

CONSTRUCTION OF 1,2,4-TRIOXANE RINGS BY PHOTO-OXYGENATION OF ENOL ETHERS AND RELATED METHODS†

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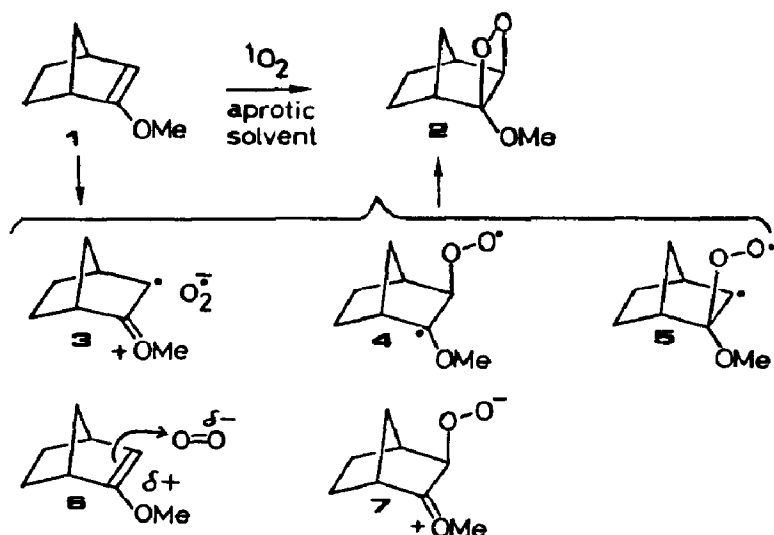
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1. Introduction

Singlet oxygen is a versatile reagent. When photo-oxygenation of an olefin is carried out in a neutral medium, hydroperoxides and 1,2-dioxetanes are formed from appropriate monoenes, whereas cisoid dienes give a Diels-Alder-type adduct [1]. Much controversy has centred on the nature of the additions, a variety of intermediates having been proposed [2]. However, little concrete evidence has been produced for their existence. Most experiments have relied on solvent effects and trapping with alcohols, while a few have exploited skeletal rearrangement as an index [3].

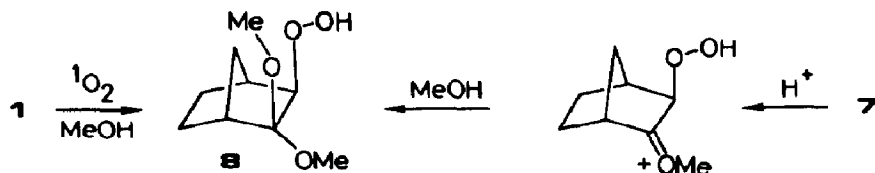
The mechanistic problem can be conveniently illustrated by 2-methoxynorbornene (1). The molecular geometry of 1 is such that singlet oxygen reacts only to give the *exo*-1,2-dioxetane (2). Although 2 can arise by a concerted [2 + 2] cycloaddition, two-step processes are also possible. Several species of varying plausibility [4] have been advanced which range from charge transfer complexes to radicals and zwitterions, *e.g.* 3 - 7:



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Our original intent was to devise experiments which would permit the interception of the precursor to the dioxetane 2 and thereby identify it.

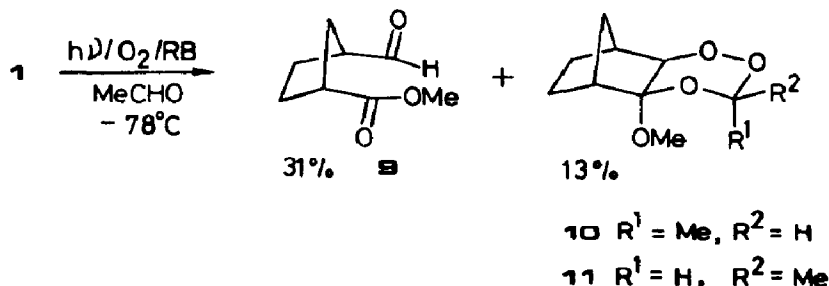
We first showed that the photo-oxygenation of 1 in methanol gave the hydroperoxy ketal 8 (among other products), which was taken as a sign of the intermediacy of the zwitterionic peroxide 7, since under the same conditions the dioxetane 2 proved to be inert [5]:



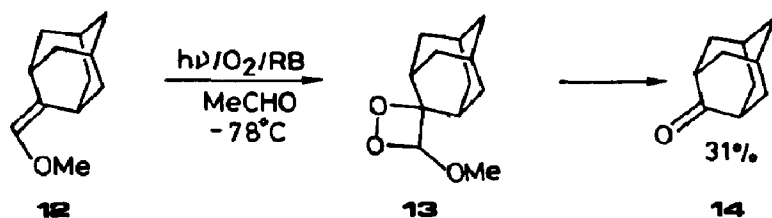
However, it has been suggested that the same result would be compatible with the radical ion pair 3 [6] or the exciplex 6 which is supposed to be solvated by methanol [7].

2. Results and discussion

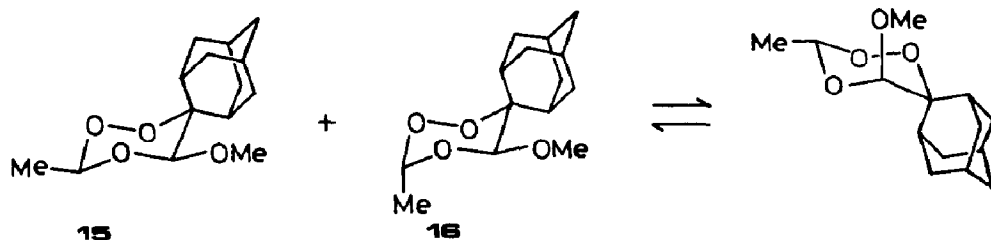
To seek further information on the intermediates 3 - 7, 2-methoxynorbornene was photo-oxygenated at -78°C in acetaldehyde. In addition to the cleavage product 9, the *cis* and *trans* trioxanes 10 and 11 were obtained in poor yield (13%):



In a similar experiment, 2-(methoxymethylidene)adamantane (12) gave, as expected, adamantanone 14, revealing that the dioxetane 13 was its precursor:

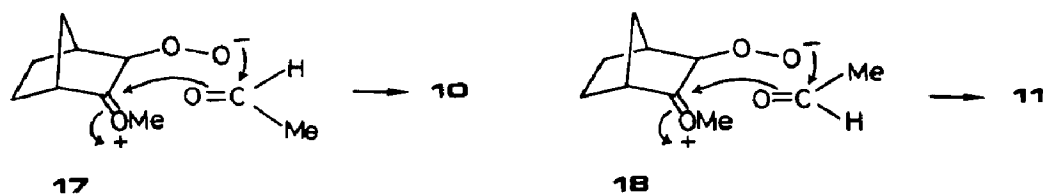


Even more revealing was the formation of the spirocyclic *erythro* and *threo* trioxanes 15 and 16 in significant amounts, 30% and 23% yields respectively [8]:



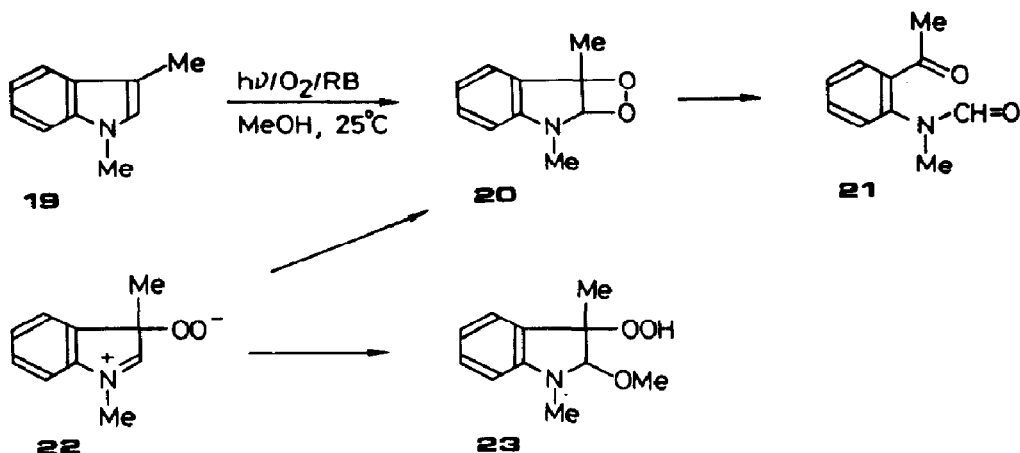
These results are best accommodated, in our opinion, in terms of a fleeting zwitterionic peroxide, which is trapped by acetaldehyde. The radical species 3 - 5 can be discarded as they would be expected to react differently with acetaldehyde. The charge transfer complex 6 could simply be a state immediately preceding the discrete species 7. 2-(Methoxymethylidene)adamantane would react in a similar fashion through its corresponding zwitterionic peroxide.

Unlike the trapping of 7 with methanol, which proceeds by protonation followed by nucleophilic attack on the methoxonium cation, acetaldehyde is captured as an electrophile. Two orientations are possible, *e.g.* 17 and 18, each of which leads to the same *cis*-fused trioxane ring, but affording a pair of diastereoisomers (10 and 11):

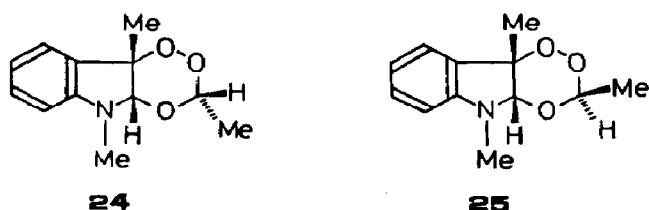


The yield of trioxane seems to depend on the lifetime of the zwitterion. Conditions or substrates which reinforce zwitterionic stability, but conserve nucleophilic properties, should favour trioxane formation.

Other stable zwitterionic peroxides have been reported for enamines [9] and indoles [10]. The behaviour of 1,3-dimethylindole (19) is typical [11]. Rose-Bengal-sensitized photo-oxygenation of 19 gave a 90% yield of the formylaminoacetophenone 21 in methanol at room temperature, arising presumably from the dioxetane 20:

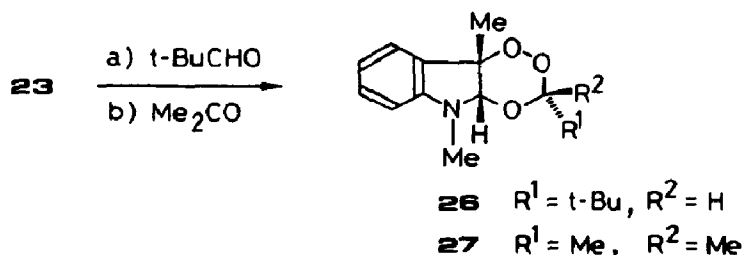


In contrast, the same experiment performed at -78°C gave an almost quantitative yield of the hydroperoxy methyl ether 23. It can be supposed that the zwitterionic peroxide 22 is formed in both cases as a primary intermediate. Normally, it collapses instantly to dioxetane 20. At low temperature, however, it survives long enough to be captured by solvent. This behaviour is paralleled when acetaldehyde is present in an inert solvent [12]. A pair of anomeric *cis*-fused trioxanes 24 and 25

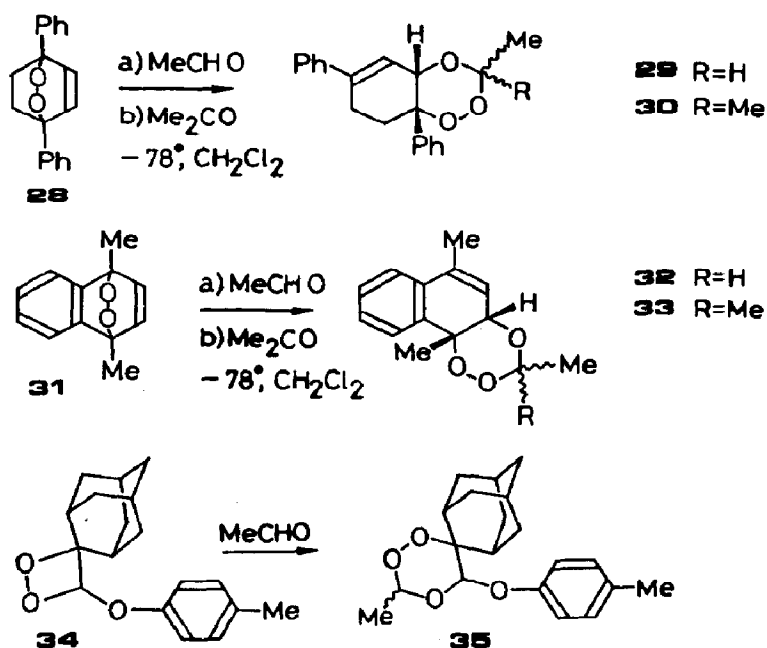


were formed in 40% and 10% yield respectively, arising from the two modes of capture of the zwitterion 22 by acetaldehyde.

An interesting extension of this mechanistic principle is provided by the hydroperoxide 23 which readily reacts with acetaldehyde, pivalaldehyde, or even acetone in the presence of an equivalent of trimethylsilyltrifluoromethanesulphonate (TMSOTf) [13] in methylene chloride. Trioxanes 24 and 25 were formed in essentially the same ratio as in the photochemical experiment, but in 60% yield. Pivalaldehyde, undoubtedly on account of its bulk, gave just the *cis* isomer 26 in 22% yield, whereas acetone afforded the gem-dimethyltrioxane 27 in 47% yield [12]:

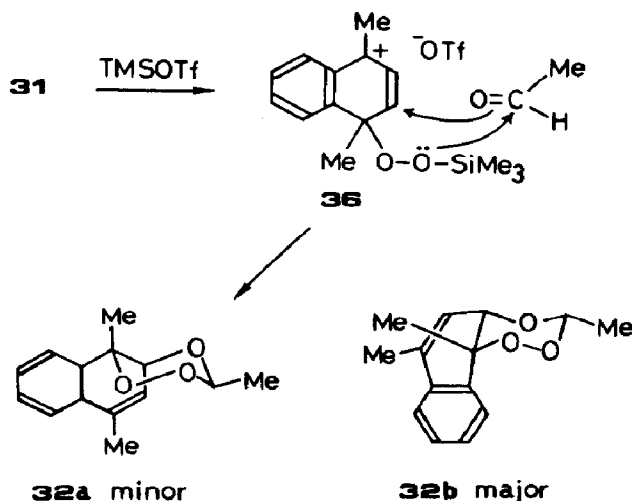


The mechanism for the catalysed condensation is not known; TMSOTf could activate either the indole hydroperoxide or the carbonyl function of the aldehyde or ketone partners. Aside from these mechanistic considerations, the same catalyst is extremely effective for the condensation of endoperoxides and dioxetanes with aldehydes and ketones to give the corresponding trioxanes [14]. Illustrations are provided by the *endo*-1,4 peroxides of 1,4-diphenylcyclohexadiene **28** and 1,4-dimethylnaphthalene **31**. Both acetaldehyde and acetone gave the *cis*-fused trioxanes **29**, **30**, **32** and **33** in better than 80% yields. The 1,2-dioxetane **34**, although it reacted well with acetaldehyde to produce trioxane **35** in high yields, none the less failed to react with acetone:



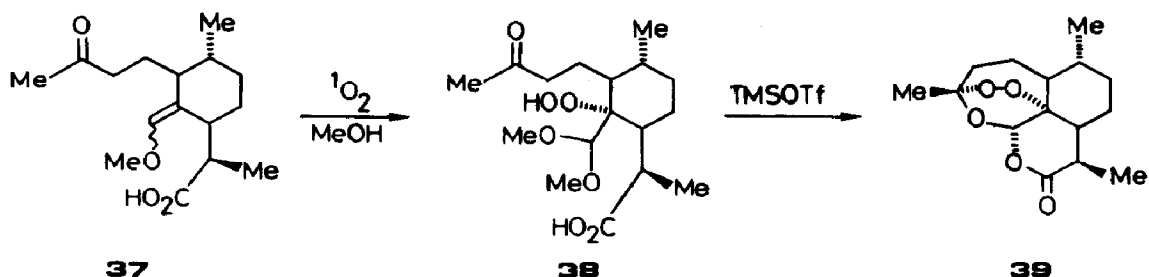
In all cases, the trioxanes are *cis* fused to the parent ring regardless of whether it is five or six membered. Clearly, the endoperoxide must initially open, presumably to give the trimethylsilyl cation species which subse-

quently attacks the carbonyl partner. For example, **31** will generate the allylic cation **36** which is constrained to incorporate acetaldehyde in the expected electronic sense but in the most geometrically convenient manner. The result is that trioxanes **32a** and **32b** adopt two different chair conformations so as to place the anomeric methyl substituent in an equatorial environment [15]:



3. Conclusions

The experiments we have described have mechanistic implications and synthetic potential. In general, it is to be expected that other zwitterionic peroxides or their formal equivalents will permit the construction of 1,2,4-trioxanes *cis* fused or spirocyclically attached to a wide variety of parent structures. Existing methods for preparing 1,2,4-trioxanes are sparse and limited in scope [16]. The new principles reported will provide greater access to this little known class of oxygen heterocycles. An important member is the naturally occurring trioxane arteannuin **39**, which is of interest as it is a potent antimalarial remedy. In the two syntheses already reported [17, 18], the key step is the photo-oxygenation of an enol ether, exemplified by **37**, followed by acid treatment which gives **39** in poor yields in both cases. Selection of the right conditions, namely the treatment of the hydroperoxy ketal **38** with TMSOTf would compensate for the poorer electrophilicity of the ketone group compared with the aldehyde function, thereby promising a better yield of **39**:



Acknowledgments

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