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CONTROLLED ANNULATION REACTIONS OF 3-METHYL-4-OXO-1-THIA-CYCLOPENT-2-ENE-1,1-DIOXIDE: A USEFUL ISOPRENOIDAL SYNTHON†

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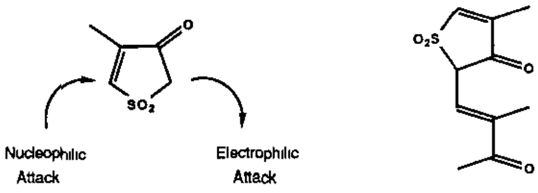
Abstract - The cyclic sulphone-enone (1) functions as a useful dienophile and dipolarophile in cycloaddition reactions to give adducts whose regiochemistry is controlled by the enone moiety. The radicophilic character of the electron deficient carbon-carbon double bond may also be used to achieve cyclopentannulation.

The beauty and simplicity of the iterative biosynthetic condensation of isopentenyl pyrophosphate with an allylic pyrophosphate for the construction of regular head to tail polyprenyl compounds has inspired the search for a wide variety of variously functionalised isoprenoid synthons.[1] Many of these biomimetic units however are specifically designed to undergo only a single type of carbon-carbon bond forming reaction and do not possess, either in the actual state or a masked form thereof, both the potentially nucleophilic and electrophilic carbon atoms situated at opposite termini of the C-5 unit which are mandatory for a synthon capable of leading to a repetitive sequence.

With these constraints in mind, we have chosen to study the chemistry of 3-methyl-4-oxo-thiacyclopent-2-ene-1,1-dioxide (1) (**Scheme 1**) as a flexible terpenoid building block. Examination of this rigid and highly functionalised system reveals that it contains both the necessary electrophilic carbon atom at C-2 and, via the derived carbanion, the nucleophilic centre at C-5. The incorporation of the trisubstituted double bond within the cyclic array also permits potentially stereospecific elaboration in terms of derived olefinic product geometry. The selection of this molecule was also dictated by the advantages of the powerfully electron withdrawing sulphone moiety which not only enhances the electrophilicity of C-2 but also facilitates inductive carbanion stabilisation at C-5, as witnessed by the pioneering studies of Julia[2] in the acyclic series, and by several recent examples involving cyclic sulphones.[3]



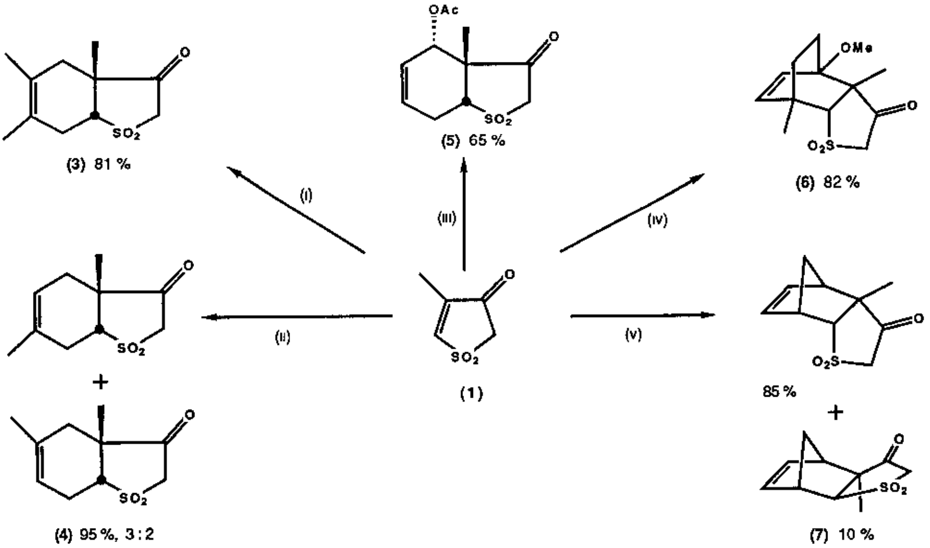
(1) (2)

Scheme 1

† Dedicated to Professor Sir Derek Barton, F.R.S., on the occasion of his 70th Birthday.

We have previously described an efficient procedure for the preparation of multigram quantities of sulphone enone (**1**) together with its fundamental regio- and stereospecific head to tail self-coupling to afford (**2**) which occurs on reaction of (**1**) with lithium diisopropylamide via an unusual single electron transfer process.[4] In the present communication, we now report our preliminary study of the ability of unit (**1**) to function as a partner in a variety of annulation sequences for the construction of rigid bicyclic systems of potential use in terpene synthesis.

In the first instance we elected to examine the sulphone-enone moiety as a dienophile in normal Diels-Alder reactions. Although simple cyclopentenones are notoriously unreactive partners in such reactions[5], we reasoned that incorporation of the sulphonyl group would enhance the necessary electron deficient nature of the double bond. The results of our study with a variety of dienes are summarised in Scheme 2 and reveal that, even in the presence of the branching alkyl group on C-3, sulphone-enone (**1**) is a highly reactive species.

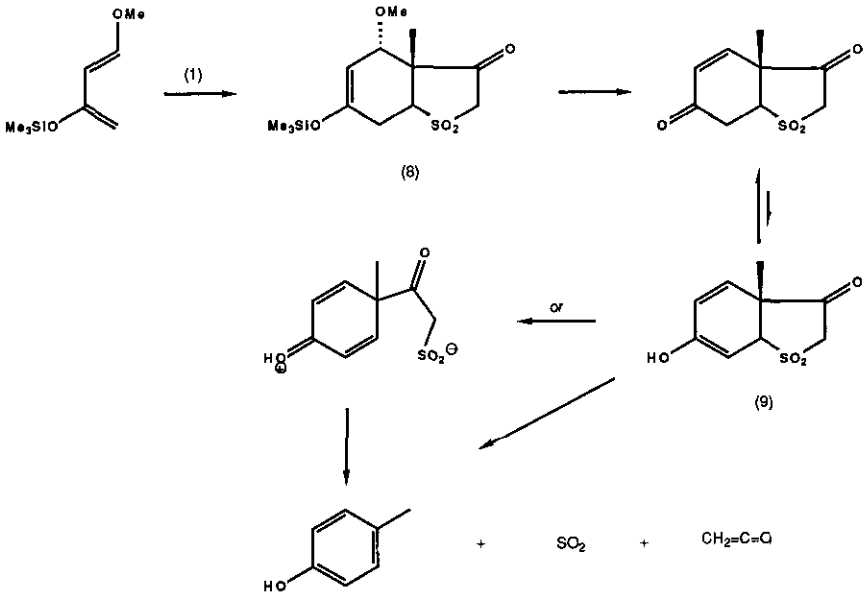


Dienes : (i) 2,3-dimethylbutadiene, (ii) isoprene, (iii) 1-acetoxybutadiene, (iv) 1-methoxy-4-methylcyclohexa-1,3-diene, (v) cyclopentadiene

Scheme 2

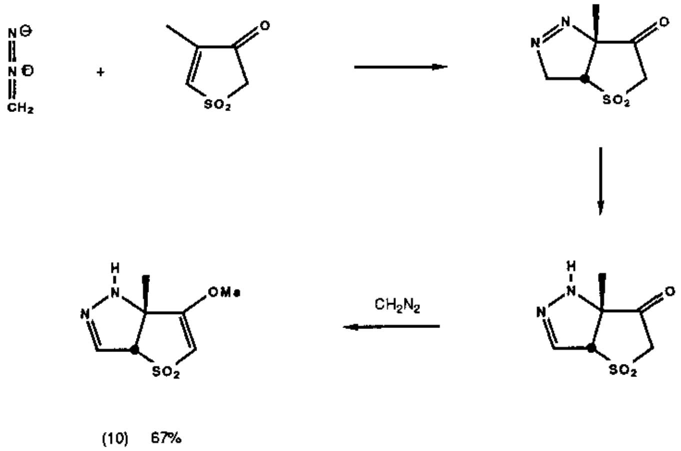
Thus, even with relatively unreactive dienes such as 2,3-dimethylbutadiene and isoprene good yields of adducts (**3**) and (**4**) respectively, may be obtained. The observed regioselectivity in the case of unsymmetrical electron rich dienes such as 1-acetoxybutadiene (adduct **5**) and 1-methoxy-4-methylcyclohexa-1,3-diene (adduct **6**) is in accord with literature precedent[6] and indicates that the mesomeric effect of the enone partner exerts a dominating influence over the inductively withdrawing sulphonyl group. The anticipated stereochemical preference for formation of endo adducts is also preserved in this system (adduct (**5**), (**6**) and (**7**)).

Interestingly, use of the Danishefsky diene led to the isolation of para-cresol in 31% yield, possibly via a mechanism involving self catalysed hydrolysis of the initially formed adduct (**8**) by the acidic protons of the β-keto sulphone unit[7] and subsequent stepwise or concerted ten electron cheleotropic extrusion of sulphur dioxide and ketene via the enol form (**9**) (**Scheme 3**).



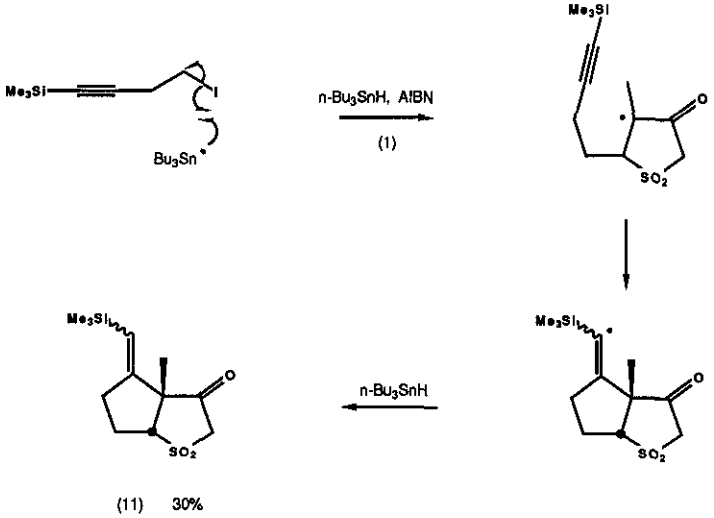
Scheme 3

We have also studied the reactivity of the sulphone-enone (1) as a dipolarophile in a prototypical 1,3-dipolar cycloaddition reaction with diazomethane (**Scheme 4**). The isolated cycloadduct (**10**) indicates once again that regioselectivity is controlled by the enone grouping and the ensuing tautomerism and formation of the methyl enol ether provides a further demonstration of the acidic autocatalysis engendered by the protons of the cyclic β-keto sulphone.



Scheme 4

Finally, in connection with a synthetic project in the terpenoid area, we wished to develop an efficient method for cyclopentannulation. A convenient solution, based on the elegant principle of multiple radical additions[8] utilised the excellent properties of sulphone-enone (1) as a radicophile for nucleophilic alkyl radicals. Accordingly, slow addition of tri-n-butylstannane containing azobisisobutyronitrile to a benzene solution of 1-trimethylsilyl-4-iodobut-1-yne led in a kinetically controlled cascade to formation of the annulated bicyclic cyclopentanoid (11) in 30% yield as a 5:1 mixture of geometrical isomers (**Scheme 5**)



Scheme 5

In summary, the exploratory annulation study described herein serves to increase the utility of 3-methyl-4-oxothiacyclopent-2-ene-1,1-dioxide (**1**) as a versatile isoprenoid synthon.

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