The Electron Transfer Induced Head to Tail Coupling Reaction of an Isoprenoidal Sulphone Enone

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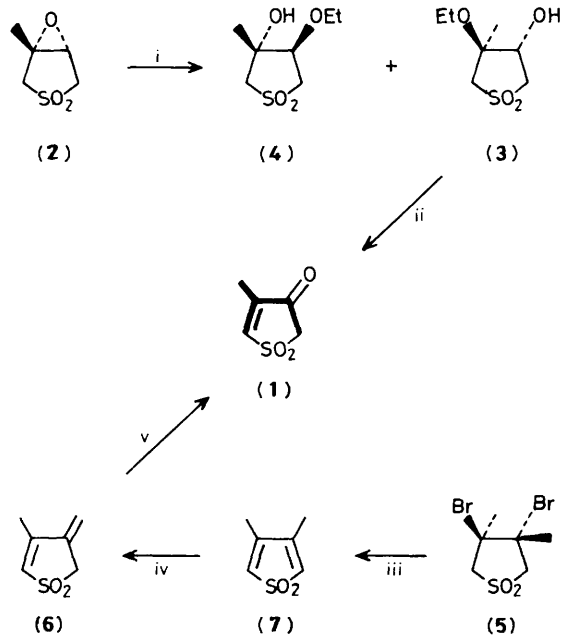
The regiospecific head to tail coupling reaction of synthon (**1**) to give (**9**) using lithium di-isopropylamide proceeds *via* a single electron transfer process.

The synthesis of terpenes from a wide variety of variously functionalised isoprenoid synthons is an attractive biomimetic concept which has been used by several research groups.[1] The powerful inductive stabilisation of a carbanion adjacent to a sulphone moiety has been particularly noteworthy in this context as demonstrated by the elegant work of Julia[2] in the acyclic series and by several recent examples involving cyclic sulphones.[3]

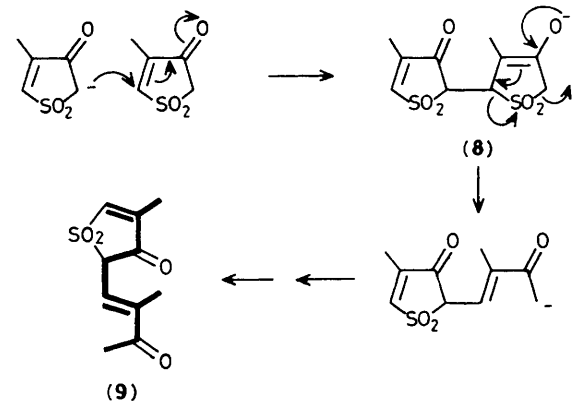
Nevertheless, a restriction of the developed methods is that, in general, the units are specifically designed to be capable of only one type of carbon–carbon bond forming reaction. Consequently, regiospecific self coupling reactions, other than *via* free radical intermediates,[4] are of limited value. Accordingly, we have chosen to explore the chemistry of the rigid and highly functionalised isoprenoid building block (**1**) which may be regarded both as a bifurcated Michael acceptor by virtue of the unsaturated sulphone–enone unit, and as a latent nucleophile using the β-keto sulphone unit. Herein, we report the fundamental head to tail self coupling reaction of unit (**1**) proceeding *via* an unusual single electron transfer (S.E.T.) process.

Compound (**1**) was initially prepared in low yield (Scheme 1) by a route[5] which required ring opening of the epoxide (**2**) with ethoxide anion to give (**3**), followed by dichromate oxidation. In contrast to the literature report,[5] we found that the major product in this reaction is the regioisomeric alcohol (**4**) (74% yield), as anticipated either by a ring opening mechanism proceeding by direct nucleophillic attack or by base induced eliminative ring opening and subsequent conjugate addition of the ethoxide anion.

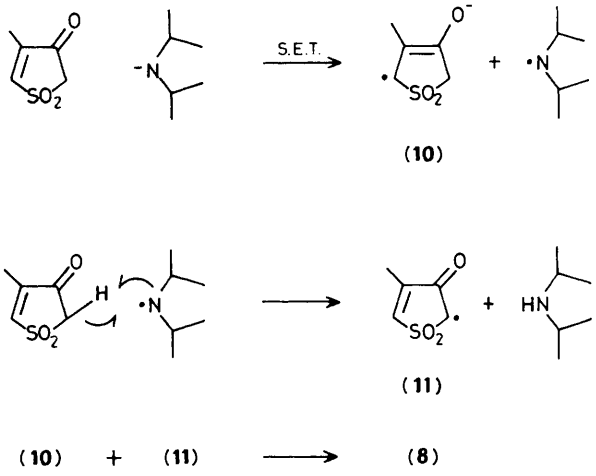
Multigram quantities of (**1**) were readily available, however, by a second sequence[6] (Scheme 1) which involved double dehydrobromination of the dibromide (**5**) followed by selective ozonolysis of the more electron rich double bond of the resultant diene (**6**). A hitherto unrecognised feature of particular interest in the dehydrobromination step is that the reaction may be cleanly stopped at an intermediate stage and the relatively rare kinetic thiophene dioxide[7] (**7**) isolated as a stable crystalline material in high yield (93% yield).



Scheme 1. *Reagents:* i, EtONa–EtOH; ii, $K_2Cr_2O_7$–H^+; iii, 1 M-NaOH, 25 °C, iv, 1 M-NaOH, reflux (72% yield); v, O_3, 25 °C (72% yield).



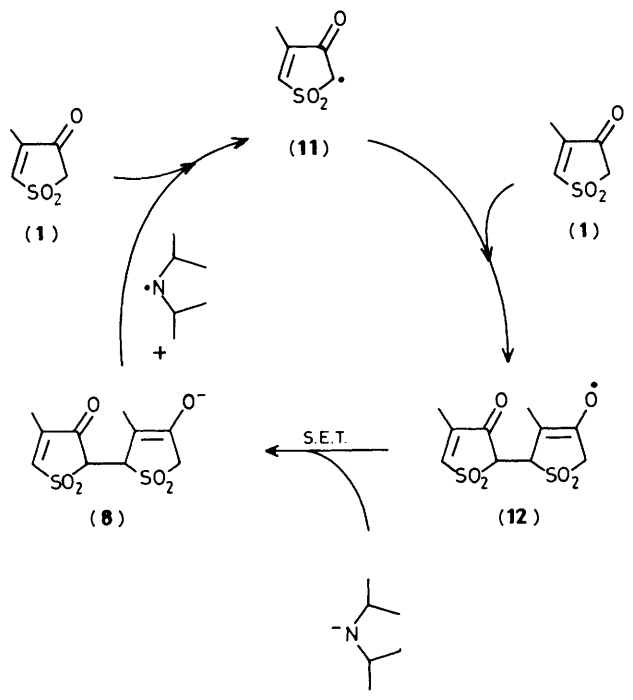
Scheme 2



Scheme 3

Attention was then focused on the development of a regiospecific self coupling reaction of sulphone enone (**1**) as envisaged in Scheme 2, wherein Michael addition of the β-keto sulphone anion is followed by cheleotropic elimination of sulphur dioxide to give, after enolate equilibration and protonation, the head to tail coupled product (**9**) containing two chemospecifically differentiated enone units. As anticipated from the high acidity constants of various cyclic β-keto sulphones[8] (*e.g.* 3,3-dimethyl-4-oxo-thiacyclopentane 1,1-dioxide, pK_a 5.83) formation of the anion is readily accomplished and the synthon (**1**) may be readily extracted into aqueous hydrogen carbonate solution and recovered on acidification. All efforts to achieve the desired reaction using classical Michael reaction catalysts such as the fluoride anion, potassium t-butoxide, sodium hydride (0.5 equiv.) in tetrahydrofuran (THF), and triphenylphosphine, under a variety of conditions, led only to recovery of starting material and/or resinous products.

Success was achieved through use of 0.5 equiv. of either dimsylsodium in dimethyl sulphoxide or lithium di-isopropylamide (LDA) in THF, both of which led directly to the coupled product (**9**) in 65 and 69% yield, respectively. The assigned configuration of the double bond in the single stereoisomer formed is supported by the absence of a nuclear Overhauser effect.



Scheme 4

The failure of classical catalysts and the unique ability of the unnecessarily powerful dimsyl and di-isopropylamide anions to achieve the desired reaction suggested to us that a single electron transfer process might be involved. Both 'bases' are known to undergo such reactions[9] and compelling evidence has been presented by Bordwell[10] that S.E.T. may be faster than kinetic deprotonation. Thus, the Michael reaction can be formally derived (Scheme 3) by a sequence involving initial electron transfer to form radical anion (**10**), precedented hydrogen atom abstraction by the resultant di-isopropylamino radical[11] from synthon (**1**), and coupling of the two radicals thus formed.

Initial support for this hypothesis was adduced by conducting a di-isopropylamide coupling reaction in the presence of an equimolar amount of *m*-dinitrobenzene as an electron scavenger, which effectively inhibited the coupling reaction.

Further evidence was available from an experiment conducted in the cavity of an e.s.r. spectrometer. A strong, persistent, and well resolved spectrum of the di-isopropylaminyl radical[12] was obtained and a control experiment served to establish that adventitious oxygen was not responsible. Interestingly however, and in opposition to the simple analysis above (Scheme 3), no signals were detected for either the radical anion (**10**) or the neutral radical (**11**).

An electron transfer mechanism which is internally consistent with the above observations may be proposed for formation of the crucial carbon–carbon bond (Scheme 4), and is in fact initiated by the production of the neutral radical (**11**) as previously outlined (Scheme 3). The propagation sequence then requires conjugate addition of (**11**) to enone (**1**) followed by S.E.T. from the di-isopropylamide anion to give intermediate (**8**), with concomitant liberation of the di-isopropylaminyl radical as a chain carrier. While S.E.T. processes in carbonyl reduction using lithium di-isopropylamide are now well recognised,[9] the present reaction is unusual in that the resultant di-isopropylaminyl radical is then used as a key element in the overall process. Under the reaction conditions

described, no significant concentrations of radicals (**11**) and (**12**) and radical anion (**10**) would therefore be anticipated. Alternative possibilities featuring loss of sulphur dioxide from radical (**12**) prior to electron transfer may also of course be considered.

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