

Stereoselective Synthesis of (*E*)- α -Hydroxy-1,3-dienes via the Reaction of 2,5-Dihydrothiophene *S,S*-Dioxides with Carbonyl Compounds

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A stereoselective synthesis of (*E*)- α -hydroxy-1,3-dienes, by thermal extrusion from adducts of 2,5-dihydrothiophene *S,S*-dioxide (**1**) with aldehydes and ketones, is presented and its extension to the synthesis of the dienone, (*E*)-tagetone, and of a 1,3,5-triene system, is illustrated.

Reaction of 2,5-dihydrothiophene *S,S*-dioxides with alkyl iodides followed by thermal desulphonylation provides a facile stereoselective method for synthesizing (*E*)-, (*E,Z*)-, and (*E,E*)-conjugated dienes.¹⁻⁴ Extension of this reaction to carbonyl compounds allows 1,3-dienes having a hydroxy group at the α -position to be synthesised stereoselectively; this functionality is present in the key intermediates in the syntheses of biologically important compounds such as compactin,⁵ mevinolin,⁶ and chlorothricolide.⁷ We report here the successful addition of α -carbanions derived from the *S,S*-dioxides (**1**) to carbonyl compounds giving the α -hydroxyalkyl derivatives (**2**) and (**3**),[†] which by subsequent desulphonylation afford α -hydroxy conjugated dienes.

The reaction of the *S,S*-dioxides (**1**) with carbonyl compounds in hexamethylphosphoramide (HMPA)-tetrahydrofuran (THF) proceeded in moderate to good yields on treatment with lithium hexamethyldisilazide (LiHMDS) in THF (see Table 1). Both aliphatic and aromatic aldehydes and ketones reacted with (**1**) to give the adducts (**2**) or (**3**). The substituent on the double bond of the *S,S*-dioxides (**1**)

profoundly affected the regioselectivity of the reaction. Thus, while an electron-donating methyl group promoted exclusive reaction at the 2-position, compound (**1b**), the presence of an electron-withdrawing phenyl substituent resulted in condensation only at C-5, compound (**1c**). Similar substituent effects have been observed in the reaction of compounds of type (**1**) with alkyl iodides.⁹

With α,β -unsaturated ketones, α -carbanions derived from (**1**) underwent conjugate addition giving predominantly the 1,4-adduct (**4**), accompanied by the 1,2-adduct (**2**) (Table 1).

The α -hydroxyalkyl compounds (**2**) and (**3**) and 1,4-adducts (**4**) thus obtained were desulphonylated (NaHCO₃, 95% EtOH, 125 °C, 30 min) to give the corresponding (*E*)- α -hydroxydienes (**5**) (X = H or Me) and (**6**) (X = Ph) and (*E*)- γ -oxo-1,3-dienes (**7**) (R² = Me, X = H or Me), respectively, with nearly 100% stereoselectivity in high yields (Table 1).

The method can be applied to the synthesis of conjugated trienes and dienones. (*E*)-2,4-Dimethylhexa-1,3,5-triene (**8**) was obtained from the adduct (**2f**) by dehydration (SOCl₂, pyridine, 75%) followed by thermal desulphonylation (NaHCO₃, CDCl₃, 125 °C, 30 min, quantitative). Taking advantage of the regioselective reaction of compound (**1b**) at the 2-position, the head position of the masked isoprene, monoterpene (*E*)-tagetone (**9**)¹⁰ was synthesized in three

[†] In previous papers, the reaction of (**1**) with aliphatic ketones under basic conditions gave no α -hydroxyalkyl derivatives, but the corresponding dehydrated or isomerized products were obtained.⁸

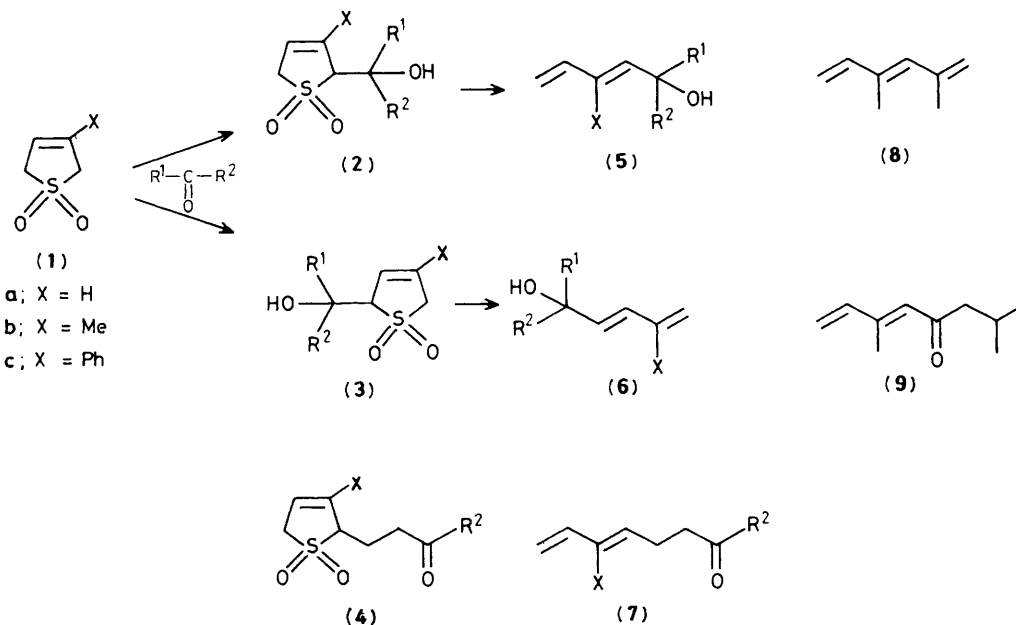


Table 1. Reaction of the *S,S*-dioxides (1) with ketones and aldehydes,^a and desulphonylation of the adducts.^b

X	R ¹	R ²	Products ^c (yield, ^d %)	
			Reaction with carbonyl compounds	Desulphonylation
H	Me	Me	(2a) (49)	(5a) (85)
H	-[CH ₂] ₅ -		(2b) (57)	
H	Me ₂ CHCH ₂	H	(2c) (62)	(5c) (87)
H	Ph	H	(2d) (42)	
H	CH ₂ =CH	Me	(2e) (9), (4e) (45)	(7e) (95)
Me	Me	Me	(2f) (75)	(5f) (84)
Me	-[CH ₂] ₅ -		(2g) (41)	
Me	Me ₂ CHCH ₂	H	(2h) (59)	(5h) (84)
Me	Ph	H	(2i) (76)	(5i) (70)
Me	Ph	Me	(2j) (34) ^e	(5j) (53) ^f
Me	CH ₂ =CH	Me	(2k) (5), (4k) (39)	(7k) (96)
Ph	Me	Me	(3l) (66)	(6l) (81)
Ph	Me ₂ CHCH ₂	H	(3m) (44)	(6m) (74)

^a A solution of LiHMDS (1.1 equiv.) in THF was added in one portion to a solution of (1) and the carbonyl compound (2 equiv.) in THF-HMPA at -78°C, and the reaction was quenched after 5 min.

^b A 95% ethanol solution of the adduct (2), (3), or (4) was heated at 125°C for 30 min in the presence of NaHCO₃ in a sealed tube. ^c All new compounds gave satisfactory spectral data. ^d Isolated yields. ^e In addition to (2j), an unidentified product (14%) was obtained.

^f Appreciable amounts of elimination products, acetophenone and isoprene, were obtained.

steps in 35% overall yield. The adduct of (1b) with isovaleraldehyde (2h) was desulphonylated to yield exclusively the (*E*)-diene (5h) which upon oxidation [pyridinium chlorochromate (PCC), CH₂Cl₂, 70%] gave (*E*)-tagetone (9).

Although a similar method for synthesizing α -hydroxy-1,3-dienes using a Diels-Alder adduct of (1), instead of using (1) directly, has been reported,¹¹ our method is advantageous in that the electronic effect of the substituent on the double bond can be transmitted to the reaction centre so that regioselective substitution at the 2- or 5-position is possible depending on the substituent.

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