A New Route to 1,3-Dienes using 3-Methylene-2,3-dihydrothiophene *S,S*-Dioxide as an Allyl Sulphone and Michael Acceptor: Synthesis of (±)-Ipsenol

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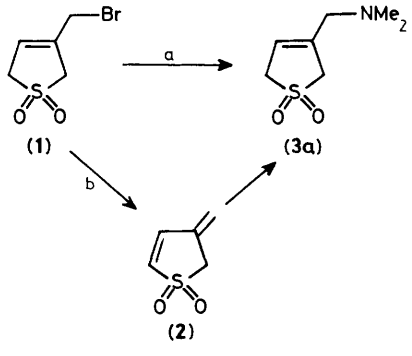
Substituted 2,5-dihydrothiophene *S,S*-dioxides, which are stable precursors of the corresponding buta-1,3-dienes, were prepared *via* reactions of 3-methylene-2,3-dihydrothiophene *S,S*-dioxide with electrophiles and nucleophiles; this method was applied to the synthesis of (±)-ipsenol.

It is well established that direct alkylation of 2,5-dihydrothiophene *S,S*-dioxides followed by desulphonylation provides a facile stereoselective method for synthesizing (*E*)-, (*E*)(*Z*)-, and (*E*)(*E*)-conjugated dienes,[1] and it has been applied to the synthesis of natural products.[2] However, these direct alkylations are limited to attaching electrophiles to the 2 or 5 positions of the *S,S*-dioxides. In a continuation of our work,[2a] it was found that 3-bromomethyl-2,5-dihydrothiophene *S,S*-dioxide (**1**)[3] reacted with dimethylamine to give 3-(*N,N*-dimethylaminomethyl)-2,5-dihydrothiophene *S,S*-dioxide (**3b**) in two competing paths: direct substitution (path a) and HBr–elimination/1,4-addition (path b) (Scheme 1).

Since the intermediate (**2**),† 3-methylene-2,3-dihydrothiophene *S,S*-dioxide, has an allyl sulphone moiety as well as an α,β; γ,δ-unsaturated sulphone moiety, we expected that it was possible to convert (**2**) into (**3**), (**4**), and (**5**) by a combination of the reactions with electrophiles and nucleophiles, and it could be a new general method for the synthesis of substituted



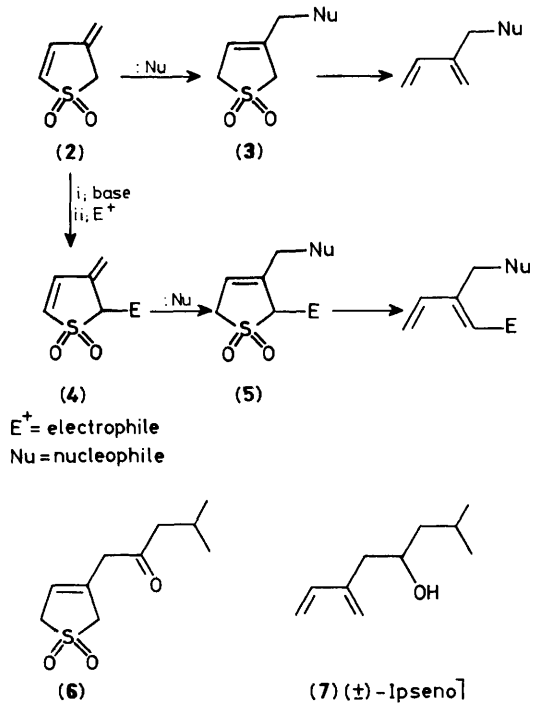
Scheme 1

† Compound (**2**) was quantitatively obtained by the treatment of (**1**) with weak base (*e.g.* di-isopropylamine, triethylamine, and K_2CO_3) in CH_2Cl_2, and was relatively unstable in neat form, but it remained in solution [^{1}H n.m.r. δ ($CDCl_3$) 7.02 (1H, d, *J* 7.0 Hz), 6.78 (1H, d, *J* 7.0 Hz), 5.57 (1H, s), 5.46 (1H, s), 3.94 (2H, s)].

Table 1. Reactions of (**2**) with nucleophiles.

Nucleophiles[a]	Additive[b]	Product (yield, %)[c]	Nu
Bu^nNH_2		(**3a**)(82)	$NHBu^n$
Me_2NH		(**3b**)(85)	NMe_2
$(CH_2)_5NH$		(**3c**)(90)	$N(CH_2)_5$
$PhNH_2$		(**3d**)(0)[d]	NHPh
HSPh	Et_3N	(**3e**)(90)	SPh
$HSCH_2CO_2Et$	Et_3N	(**3f**)(84)	SCH_2CO_2Et
$MeNO_2$	DBU	(**3g**)(42)	$CH_2(NO_2)$
Pr^nNO_2	TMG	(**3h**)(43)	$CH(NO_2)Et$
$Me_2CHCH_2CH_2NO_2$	TMG	(**3i**)(50)	$CH(NO_2)CH_2CHMe_2$
$PhCH_2NO_2$	TMG	(**3j**)(45)	$CH(NO_2)Ph$
Me_2CHNO_2	TMG	(**3k**)(78)	$C(NO_2)Me_2$

[a] Amines (10 equiv.), thiols (1.5 equiv.), and nitro-compounds (2 equiv.) were used. [b] 1 equiv. [c] Isolated yield. [d] Compound (**3d**) was obtained by the reaction of (**1**) with aniline *via* direct substitution in 90% yield.



Scheme 2

buta-1,3-dienes (Scheme 2).‡ We report here a convenient method for the synthesis of a variety of substituted 2,5-dihydrothiophene *S,S*-dioxides using (**2**) as an allyl sulphone and Michael acceptor.

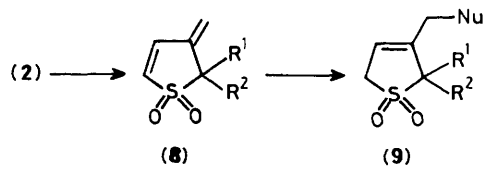
Compound (**2**) reacted with aliphatic amines to produce the corresponding (**3a—c**) in good yield, and reacted with thiols to give (**3e,f**) in the presence of triethylamine at room temperature (Table 1). Reactions of (**2**) with alkyl-lithium and Grignard reagents led to the decomposition of (**2**) because of the basic properties, and none of the adducts was obtained. Successful introduction of carbon nucleophiles to the exo-methylene group of (**2**) was achieved by reaction of (**2**) with nitro-compounds in MeCN using 1,1,3,3-tetramethylguanidine (TMG)[4] at room temperature or 1,8-diazabicyclo-

‡ When (**1**) was subjected to direct alkylation, HBr–elimination occurred immediately.

Table 2. Reactions of (**8**) with nucleophiles.

(**8**)	Nucleophiles	Additive[a]	Product (yield, %)[b]	R^1	R^2	Nu
a	Me_2NH		(**9a**)(88)	Me	H	NMe_2
a	$(CH_2)_5NH$		(**9b**)(80)	Me	H	$N(CH_2)_5$
b	Me_2NH		(**9c**)(95)	Me	Me	NMe_2
b	$(CH_2)_5NH$		(**9d**)(85)	Me	Me	$N(CH_2)_5$
b	HSPh	Et_3N	(**9e**)(56)	Me	Me	SPh
b	Me_2CHNO_2	TMG	(**9f**)(61)	Me	Me	$C(NO_2)Me_2$

[a] 1 equiv. [b] Isolated yield.



Scheme 3

[5.4.0]undec-7-ene (DBU)[5] at 0 °C as the base, and the corresponding (**3g—k**) were obtained in moderate to good yield. Similar results were obtained by the reaction of (**1**) with nitro-compounds using 2 equiv. of base *via* HBr–elimination/1,4-addition.

Owing to the versatility of the nitro group, nitro-compounds act as useful synthetic intermediates, and this method was applied to the synthesis of (±)-ipsenol,[6] the principle components of the aggregation pheromone of bark beetles (*e.g. Ips confusus*). The nitro-compound (**3i**) was converted into the corresponding carbonyl compound (**6**) by hydrogen peroxide/potassium carbonate[7] in 50% yield. The reduction of (**6**) ($NaBH_4$ in methanol) followed by thermal desulphonylation in a sealed tube ($NaHCO_3$, $CDCl_3$, 125 °C, 3 h, quantitative) gave (±)-ipsenol (**7**).

Compound (**2**) was allowed to react with electrophiles in the following manner. Compound (**8a**) was obtained by the addition of lithium hexamethyldisilazide (LiHMDS) (1 equiv.) in tetrahydrofuran (THF) to a solution of (**2**) (2 equiv.) and MeI (2 equiv.) in THF at −78 °C in 80% yield. Interestingly, the *gem*-dianion[8] of (**2**) is rather stable, whereas the monoanion of (**2**) is unstable at −78 °C. When (**2**) was added to LiHMDS (2 equiv.) in THF at −78 °C, and then treated with MeI (2 equiv.), (**8b**) was produced in 90% yield.

The reactions of (**8**) with nucleophiles gave corresponding 2,3- and 2,2,3-substituted 2,5-dihydrothiophene *S,S*-dioxides (**9**) (Table 2).

In this way, 3-methylene-2,3-dihydrothiophene *S,S*-dioxide (**2**) acted as a synthetic equivalent of isoprene, and was converted to substituted 2,5-dihydrothiophene *S,S*-dioxides (**9**) *via* electrophilic substitution and nucleophilic addition.

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