

Novel Formation of Dienes with Greater Steric Congestion resulting from the Diels–Alder Reaction–Desulfonylation Sequence of 4-Acyl-4*H*,6*H*-thieno[3,4-*c*]furan 5,5-Dioxides

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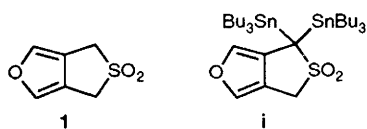
4-Acyl-4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxides have been prepared and submitted to Diels–Alder reactions to afford dienes with greater steric congestion after desulfonylation.

The furan-annulated sulfolene, 4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxide **1**,¹ contains furan and 3-sulfolene² moieties, both of which can be used as the diene component in Diels–Alder reactions. This means that **1** could sequentially react with two different kinds of dienophiles and offer a rapid elaboration of variously substituted multicyclic systems. Also **1** can be seen as a 3,4-dimethylenefuran³ synthon. Because **1** is a stable compound and should be easily functionalized on both furan and 3-sulfolene moieties, it should be synthetically valuable. We have already shown that **1** reacts with activated alkenes on either moiety selectively and is readily converted to the 4-alkylated derivatives; appropriate derivatives with unsaturated side chains undergo intramolecular Diels–Alder reactions to afford fused furans in good yields.¹

In order to demonstrate the applicability of **1** as a synthetic building block, we further investigated the chemical modifications of **1** at the position α to the SO₂ group and submitted the resulting derivatives to Diels–Alder reactions. We now report that the predominant formation of dienes with greater steric

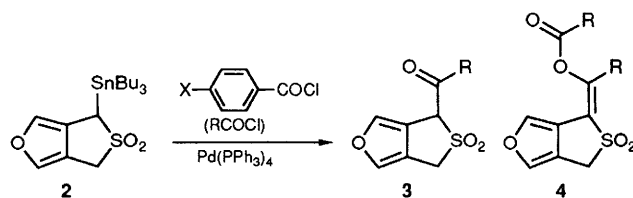
congestion resulted from Diels–Alder reaction followed by desulfonylation. These sterically congested dienes may have use as precursors in the synthesis of biologically active compounds such as vitamin D.

We planned to prepare derivatives by cross coupling reactions.⁴ The stannane **2** was obtained in 53% yield from **1** by metallation with LiN(SiMe₃)₂ (LiHMDS) (1.0 equiv.) in THF^{†‡} at –105 °C for 10 min, followed by trapping with tributyltin chloride. [The distannane **i** (13%) and **1** (29%) were also obtained.] The stannane **2** was stable enough to be purified by silica gel chromatography and fully characterized by spectroscopic means (¹H NMR, MS, and HRMS). Acylation of **2** with some various chlorides in the presence of Pd(PPh₃)₄ catalyst (2.5 mol%) gave 4-acyl derivatives **3** in *ca.* 51% yields along with the double acylation products **4**⁵ (Table 1). These results were rather disappointing. Further, electrophiles, aryl halides and vinyl halides, could not undergo the

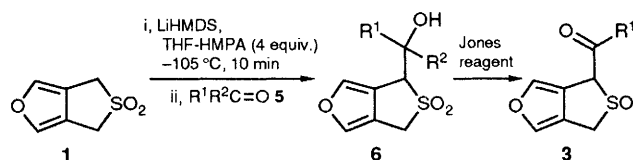


[†] Addition of HMPA resulted in a drastically reduced yield of **2**.

[‡] THF = tetrahydrofuran; HMPA = hexamethylphosphoric triamide; PDC = pyridinium dichromate; PCC = pyridinium chlorochromate; DMAD = dimethyl acetylenedicarboxylate; LiHMDS = lithium hexamethyldisilazide

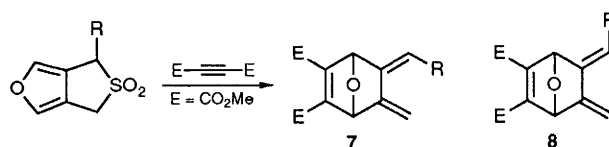
Table 1 Cross coupling reactions of **2** with acid chlorides

Entry	X	Solvent	t/h	Temp.	3 (%)	4 (%)	1 (%)
1	H	HMPA	3	0 °C	51	—	14
2	NO ₂	HMPA	0.5	0 °C	—	33	14
3	OMe	HMPA	3	Room temp.	36	—	25
4	Cl	HMPA	3	Room temp.	37	—	22
5	AcCl	HMPA	2	0 °C	38	5	15

Table 2 Aldol reactions of 4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxide **1** followed by oxidation

Entry	5	Product	Yields of 6 (%)	1 (%)	Product	Yield of 3 (%)
1	PhCHO	6a	62 (1.3:1) ^c	17	3a	72
2	<i>c</i> -HexCHO ^a	6b	71 (3.2:1)	12	3b	80
3 ^b	<i>c</i> -HexCHO ^a	6b	44 (2.0:1)	46		
4	EtCHO	6c	63 (1.7:1)	33		
5	Me ₂ CHCH ₂ CHO	6d	55 (1.8:1)	36		
6	Me ₂ CO	6e	63	23		

^a *c*-Hex = cyclohexyl. ^b LiHMDS was added to **1** in THF-HMPA in the presence of **5** at -78 °C. ^c Diastereoisomer ratio.

Table 3 Diels-Alder reactions of 4-substituted-4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxides^a

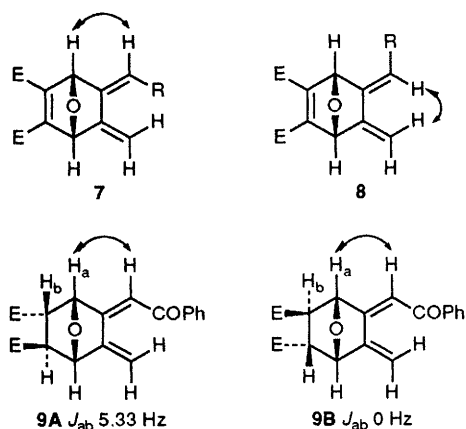
R	Dienophile	T/°C	t/h	Products, yield (%)
PhCO	3a EC≡CE	120	6	7a, 8a , 79 (5.4:1)
PhCO	3a (<i>E</i>)-ECH=CHE	100	20	9A, 9B , 47 (1.4:1)
<i>c</i> -HexCO	3b EC≡CE	130	3	7b, 8b , 95 (4.7:1)
Bu	10 EC≡CE	80	2.5	7c, 8c , 54 (1:2.0)
EtCO ₂	11 EC≡CE	120	4	7d , 67; 8d , 20
EtCO ₂	11 AcCH=CH ₂	110	10	12 , 83; 13 , 11
EtCO ₂	11 AcCH=CH ₂ ^b	-78	3	12 , 12; 13 , 78 (<i>C</i> 54%) ^c

^a In benzene unless otherwise noted. ^b In CH₂Cl₂ with TiCl₄. ^c *C* = chelation control.

coupling reaction with **2**. We searched for other methods for acylation reactions. The reaction of the anion generated from **1** (LiHMDS, THF, -105 °C) with benzoyl chloride gave only **4** (11%) and **1** (23%). Finally aldol reaction followed by oxidation was found to give acyl derivatives in satisfactory yields. When a solution of **1** in THF-HMPA (4 equiv.) was successively treated with LiHMDS (1.0 equiv.) for 10 min, then 1.5 equiv. of an aldehyde, the aldol products **6** were obtained in good yields (Table 2, entries 1, 2, 4-6) (diastereoisomer ratio 1.3-3.2:1, separable). After getting the

aldol products, we studied the oxidation of **6a**. PDC did not give any products. PCC oxidation did not go to completion and gave **3a** in only 44% yield along with **6a** (45%). Swern oxidation gave dehydrated compounds. Finally, Jones reagent oxidized **6a** satisfactorily to afford the benzoyl derivative **3a** in 72% yield. Compound **6b** was oxidized in the same way to give **3b** in good yield (Table 2).

Next we attempted Diels-Alder reactions. When a benzene solution of **3a** was heated at 120 °C with DMAD (3 equiv.) in a sealed tube, the Diels-Alder reaction followed by desulfonyl-



Scheme 1 NOEs observed

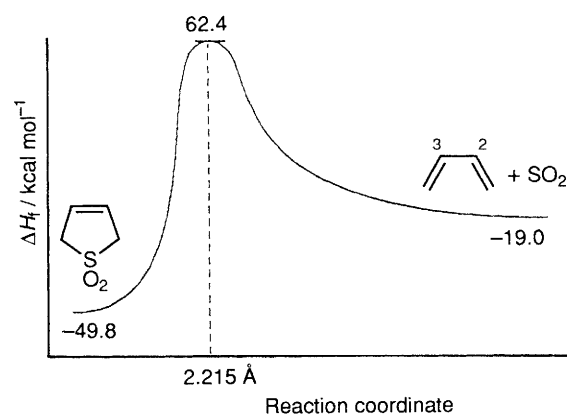
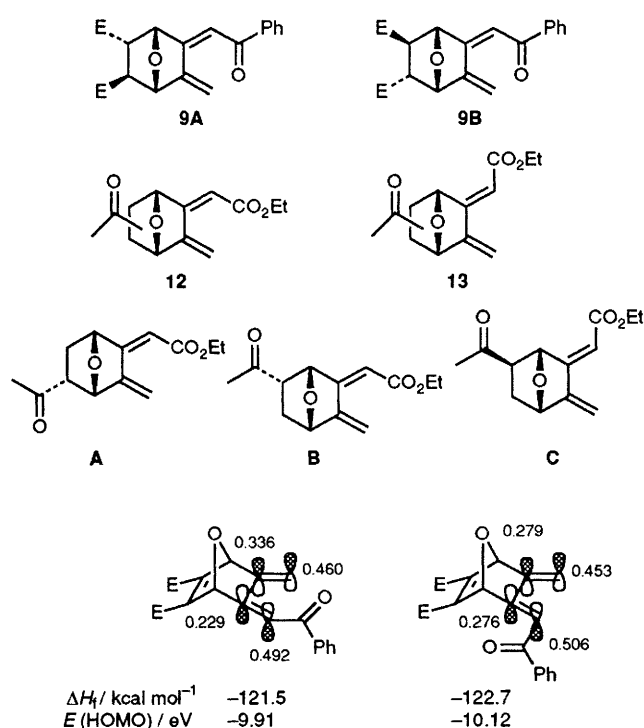
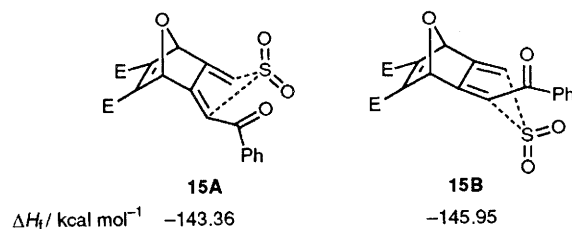


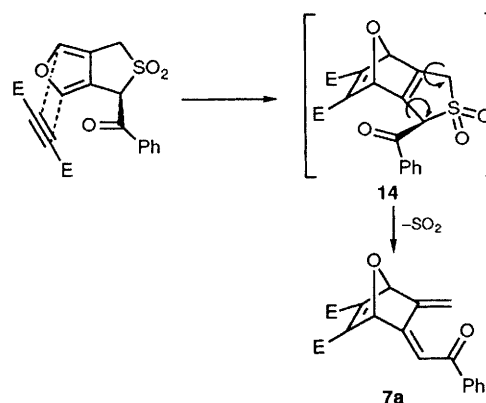
Fig. 1 Reaction profile for desulfonylation of 3-sulfolene



Scheme 2 MNDO-PM3 calculations on 7a and 8a; 1 cal = 4.184 J



Scheme 3 MNDO-PM3 calculations on 15A and 15B



Scheme 4 Mechanism of Diels-Alder reaction

ation occurred to afford mono-adducts, 7a and 8a, as an inseparable mixture in 79% yield (5.4:1) (Table 3). The structures of 7a and 8a were determined by ¹H NMR spectroscopy. NOEs were observed as indicated by arrows in Scheme 1. To our surprise, the (*E*)-isomer 7a was formed predominantly. The cyclohexylcarbonyl compound 3b and ester 11§ also gave the (*E*)-isomers 7b and 7d as the main products, respectively. The predominant formation of the (*E*)-isomers, which are more sterically congested than the (*Z*)-compounds, is novel.⁶ The butyl derivative 10¹ reacted with DMAD to afford mainly the (*Z*)-isomer 8c (7c:8c = 1:2.0, 54%) along with bis-adducts (two isomers in 1:0.9 ratio, 16%) (Table 3). These differences probably arise from the reactivities of the product dienes 7a and 7c. The more reactive 7c reacts with both SO₂ and the dienophile to give the more stable product 8c and bis-adducts under the reaction conditions.

The reaction of 7a with dimethyl fumarate gave only the (*E*)-isomers 9A and 9B (1.4:1). Neither (*Z*)-isomer nor bis-adduct was observed. The ester 11 reacts with methyl vinyl ketone at 110 °C in a sealed tube to give (*E*)-isomers 12 in 83% yield (A 40%, B 31%, *exo*B 5%, *exo*A 5%) along with (*Z*)-isomers (11%).

We have carried out semiempirical MO calculations on these unusual selectivities for information on the diene geometries. First, the structures of both (*E*)- and (*Z*)-dienes, 7a and 8a, were fully optimized by the MNDO-PM3⁷ method (Scheme 2). The main product 7a is actually less stable than the (*Z*)-diene 8a by 1.2 kcal mol⁻¹ as we expected. Next we focused our attention on the mechanism of desulfonylation of intermediate 14. It is well known that the cheletropic reaction of 3-sulfolene proceeds in a disrotatory mode.⁸ However, there is no information about its transition state, so we performed a model study on the desulfonylation of 3-sulfolene. We calculated its energies at fixed S-X [X is the centre of C(2)-C(3)] distances while optimizing all other variables.

§ The ester 11 was prepared in 89% yield by treating 1 in THF-HMPA (4 equiv.) with LiHMDS (2.0 equiv.) in the presence of NCCO₂Et at -78 °C.

The reaction profile for the desulfonylation is illustrated in Fig. 1, which shows that the transition state of desulfonylation has an S–X distance of 2.215 Å. We used this value as the distance in the transition state for desulfonylation of **14**. Sulfur dioxide was placed over and under the diene plane of **7a** and the energies were recalculated (Scheme 3). The structure **15B** is more stable than **15A** by 2.6 kcal mol⁻¹. This means that SO₂ is eliminated under the diene plane of **7a**. Also it is reasonable to postulate that the Diels–Alder reaction occurs from the less hindered face of furan to give **14** (Scheme 4). The experimental results for the Diels–Alder reaction of **3a** could be reasonably explained by the above mechanism.

All new compounds described in this paper were characterized by ¹H NMR, MS and HRMS.

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