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

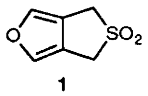
Kaori Ando,[a] **Chiharu Hatano,**[a] **Naoki Akadegawa,**[a] **Atsushi Shigihara**[b] **and Hiroaki Takayama***[a]

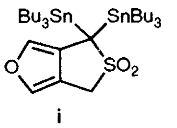
[a] *Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan*
[b] *Hoshi College of Pharmacy, Shinagawa, Tokyo 142, Japan*

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-sulfolene[2] 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-dimethylenefuran[3] 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 SO_2 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.


1


i

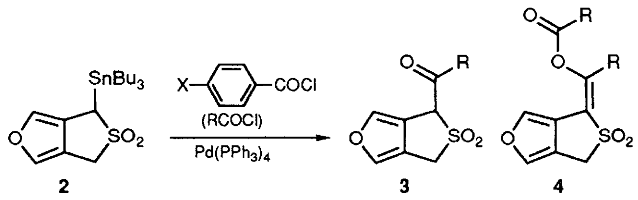
We planned to prepare derivatives by cross coupling reactions.[4] The stannane **2** was obtained in 53% yield from **1** by metallation with $LiN(SiMe_3)_2$ (LiHMDS) (1.0 equiv.) in THF†‡ at −105 °C for 10 min, followed by trapping with tributyltin chloride. [The distannane **i** (13%) and **1** (29%) 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 $Pd(PPh_3)_4$ 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**.

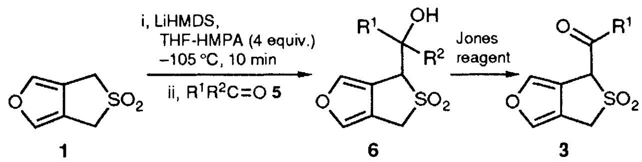
‡ THF = tetrahydrofuran; HMPA = hexamethylphosphoric triamide; PDC = pyridinium dichromate; PCC = pyridinium chlorochromate; DMAD = dimethyl acetylenedicarboxylate; LiHMDS = lithium hexamethyldisilazide

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

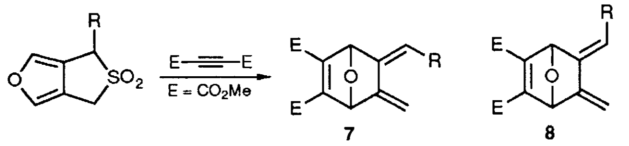
Table 2 Aldol reactions of 4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxide **1** followed by oxidation



Entry	**5**	Product	Yields of **6** (%)	**1** (%)	Product	Yield of **3** (%)
1	PhCHO	**6a**	62 (1.3 : 1)[c]	17	**3a**	72
2	c-HexCHO[a]	**6b**	71 (3.2 : 1)	12	**3b**	80
3[b]	c-HexCHO[a]	**6b**	44 (2.0 : 1)	46		
4	EtCHO	**6c**	63 (1.7 : 1)	33		
5	Me_2CHCH_2CHO	**6d**	55 (1.8 : 1)	36		
6	Me_2CO	**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]

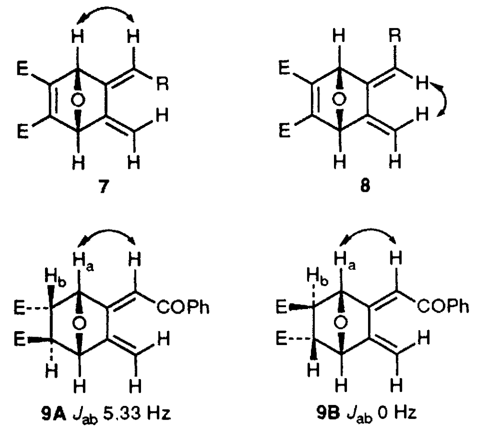


R		Dienophile	*T*/°C	*t*/h	Products, yield (%)
PhCO	**3a**	EC≡CE	120	6	**7a**, **8a**, 79 (5.4 : 1)
PhCO	**3a**	(*E*)-ECH=CHE	100	20	**9A**, **9B**, 47 (1.4 : 1)
c-HexCO	**3b**	EC≡CE	130	3	**7b**, **8b**, 95 (4.7 : 1)
Bu	**10**	EC≡CE	80	2.5	**7c**, **8c**, 54 (1 : 2.0)
$EtCO_2$	**11**	EC≡CE	120	4	**7d**, 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 (*C* 54%)[c]

[a] In benzene unless otherwise noted. [b] In CH_2Cl_2 with $TiCl_4$. [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

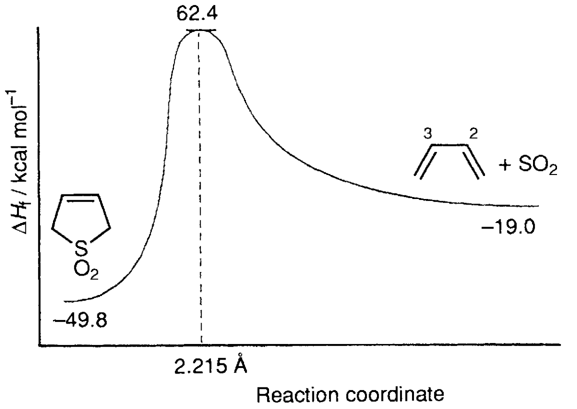
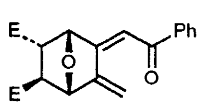
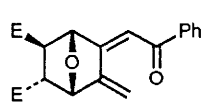


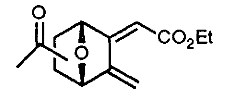
Fig. 1 Reaction profile for desulfonylation of 3-sulfolene



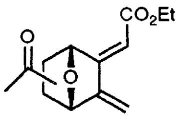
9A



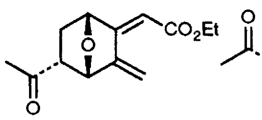
9B



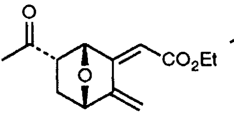
12



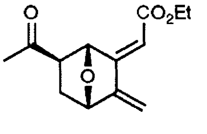
13



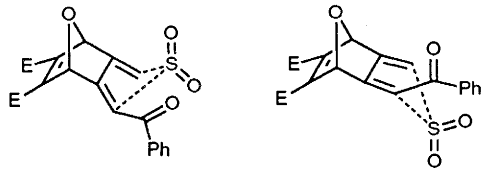
A



B

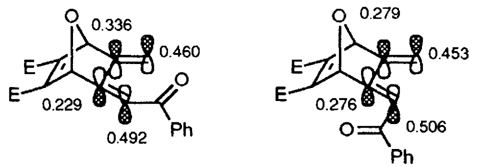


C



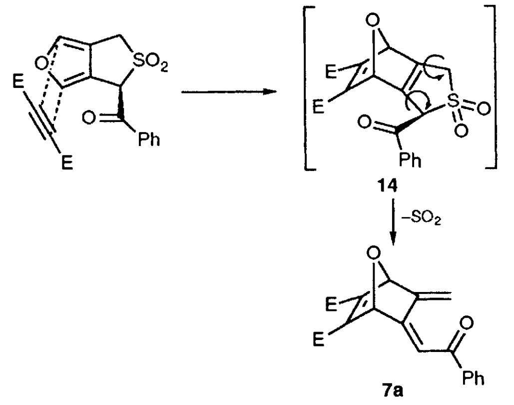
	15A	15B
ΔH_f/ kcal mol^{-1}	−143.36	−145.95

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



ΔH_f/ kcal mol^{-1}	−121.5	−122.7
E(HOMO) / eV	−9.91	−10.12

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



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 ^{1}H 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 **10**[1] 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 SO$_2$ 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-PM3[7] 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 NCCO$_2$Et 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 SO_2 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.

This work was partially supported by a Grant-in-Aid for Young Scientists No. 03771695 from the Ministry of Education, Science, and Culture of Japan.

Received, 17th February 1992; Com. 2/00825D

References

1 K. Ando, N. Akadegawa and H. Takayama, *J. Chem. Soc., Chem. Commun.*, 1991, 1765; T. Suzuki, K. Kubomura, H. Fuchii and H. Takayama, *J. Chem. Soc., Chem. Commun.*, 1990, 1687.

2 S. Yamada and H. Takayama, *Yuki Gosei Kagaku Kyokai Shi* (*J. Synth. Org. Chem. Jpn.*), 1988, **46**, 893; S. Yamada, H. Ohsawa, T. Suzuki and H. Takayama, *J. Org. Chem.*, 1986, **51**, 4934; S. Yamada, H. Suzuki, H. Naito, T. Nomoto and H. Takayama, *J. Chem. Soc., Chem. Commun.*, 1987, 332; H. Takayama and T. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1988, 1044.

3 K. J. Stone, M. M. Greenberg, S. C. Blackstock and J. A. Berson, *J. Am. Chem. Soc.*, 1989, **111**, 3659 and references cited therein.

4 D. Milstein and J. K. Stille, *J. Org. Chem.*, 1979, **44**, 1613; J. W. Labadie and J. K. Stille, *J. Am. Chem. Soc.*, 1983, **105**, 6129.

5 The formation of only double acylation products has been reported in a direct deprotonation–acylation sequence of 3-sulfolene: T. Chou, H. Tso and L. C. Lin, *J. Org. Chem.*, 1986, **51**, 1000.

6 A similar compound was prepared by the Ramberg–Bäcklund reaction in 49% yield, but only the (*Z*)-diene was obtained: E. Block and D. Putman, *J. Am. Chem. Soc.*, 1990, **112**, 4072.

7 MOPAC-Vesion 5. J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209.

8 W. L. Mock, *J. Am. Chem. Soc.*, 1975, **97**, 3666.