SYNTHESES OF 2-SUBSTITUTED FURAN-ANNULATED 3-SULFOLENES AND THEIR DIELS-ALDER REACTIONS

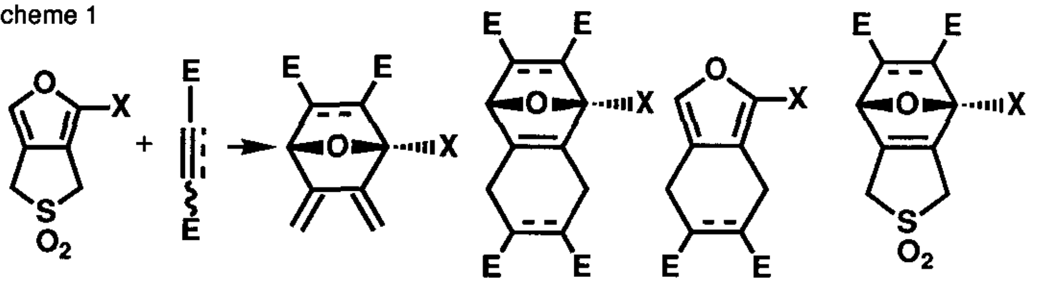
*Takayoshi Suzuki, Hideyuki Fuchii,and Hiroaki Takayama**

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan

Abstract-----The preparation of 2-substituted 4,6-dihydrothieno[3,4-*c*]furan-5,5-dioxides (**1b-e**) and their intermolecular Diels-Alder reactions with typical dienophiles are described.

Furan-annulated 3-sulfolene (**1a**; X=H) appears to be a useful masked bis-diene exhibiting versatility in Diels-Alder reaction. Thus, depending on the reaction conditions and dienophiles, **1a** sequentially reacted with dienophiles to produce four types of cycloadducts: a monocycloadduct bearing bis-*exo*methylenes (type A), a tandem-adduct (type B), a monocycloadduct containing a furan ring (type C), and a monocycloadduct with a 3-sulfolene ring (type D).[1a,b] As continuation of our studies on the chemistry of furansulfolene for the syntheses of variously substituted polycyclic molecules,[1c] we investigated the reactivity of its furan moiety having substituents at the 2-position. In the following is reported the preparation of **1b-e** and the results of Diels-Alder reaction (Scheme 1).

Scheme 1



	Dienophile	Type A	Type B	Type C	Type D
1 a;X=H	alkyne	2	3	4	
b;X=Br	alkene	6	7	8	

c;X=Ac

d;X=NO_2

e;X= *p*-MeO-C_6H_4

E=COOMe

Table I Reaction of Furansulfolenes (**1b**-**e**) with Dienophiles at 120 °C

				Products (Isolated Yield, %)				
Entry	Sulfolene	Dienophile	React. Time (h)	Type A	Type B	Type C	Others	Total Yield (%)
1	**1b** (X=Br)	**DMAD**[a]	4.5	**2b** (58)	**3b** (17)			75
2	**1c** (X=Ac)	**DMAD**	6.0	**2c** (14)	**3c** (57)	**4c** (16)		87 (10)[b]
3	**1d** (X=NO_2)	**DMAD**	24.0				**5d** (14)	14
4	**1e** (X=Ar[c])	**DMAD**	4.5	**2e** (31)	**3e** (27)			58
5	**1b**	**DM**[d]	22.0	**6b** (*endo* 49) (*exo* 4)				53
6	**1c**	**DM**	24.0	**6c** (*endo* 13) (*exo* 4)				17 (70)[b]
7	**1d**	**DM**	24.0	**6d** (*endo* 10)				10
8	**1b**	**DF**[e]	20.0	**6b** (5-*exo*,6-*endo* 13) (5-*endo*,6-*exo* 7)		**8b** (11)		31
9	**1c**	**DF**	20.0	**6c** (5-*exo*,6-*endo* 7) (5-*endo*,6-*exo* 5)		**8c** (10)		22 (73)[b]
10	**1d**	**DF**	24.0			**8d** (11)		11

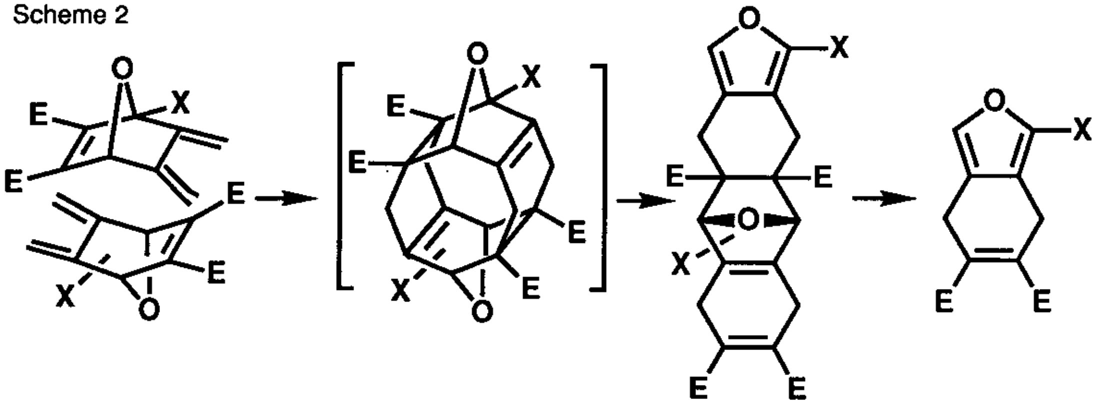
a) DMAD=dimethyl acetylenedicarboxylate. b) Recovery of the furansulfolene. c) Ar=*p*-MeO-C_6H_4-. d) DM=dimethyl maleate. e) DF=dimethyl fumarate.

The best yield (35%) of bromofuransulfolene (**1b**; amorphous) was obtained on treating **1a** with the Br_2-dioxane complex in dioxane at 50 °C for 1.5 h.[2] The facile acetylation of **1a** with acetic *p*-toluenesulfonic anhydride, prepared conveniently from acetyl chloride and silver *p*-toluenesulfonate[3], in acetonitrile at 50 °C for 9 h gave acetylfuransulfolene (**1c**; mp 132 -134 °C) in 80% yield. A simple method for generating nitronium triflate from nitronium tetrafluoroborate and silver triflate afforded a 37% nitration of **1a** to nitrofuransulfolene (**1d**;

mp 194 -196 °C) at -40 °C for 1.5 h.[4] The tetrakis(triphenylphoshine)palladium(0)-catalyzed cross coupling reaction of **1b** with *p*-methoxyphenyl(trimethyl)tin[5] in dioxane at 105 °C proceeded smoothly to afford phenylfuransulfolene (**1e**; amorphous) in 57% yield. The structures of all new furansulfolenes were confirmed by spectral data.[6]

The Diels-Alder reaction of bromofuransulfolene (**1b**) with dimethyl acetylenedicarboxylate (DMAD; 3 equiv.) was carried out at 120 °C (benzene; sealed tube) to afford two types of cycloadducts, bismethylene type **2b** (58%) and tandem type **3b** (17%) in 75% total yield (Entry 1). The same treatment of non-substituted **1a** with DMAD gave bismethylene type **2a** (62%) and tandem type **3a** (29%) in 91% total yield,[1a] bromo substitution on furan ring thus apparently has no effect on the reactivity of **1a**. A similar reaction of phenyl-substituted **1e** with DMAD produced the same type adducts (**2e**) and (**3e**), containing the required skeletal features of lignan lactones of the podophyllotoxin series (Entry 4).[7] In the case of acetylfuransulfolene (**1c**), three DMAD adducts, **2c** (14%), **3c** (57%) and monocycloadduct (**4c**) (16%) were obtained in unexpectedly high total yield (87%) and **1c** was recovered at 10% (Entry 2). Although it is well known that 2-acetylfuran does not undergo Diels-Alder reaction with any dienophile to afford a cycloadduct,[8] in our case, desulfonylation of the initially formed type D adduct to type A adduct appeared to circumvent the unfavorable equilibrium between the 2-substituted furansulfolene and its type D adduct and consequently, the acetyl substituent did not hinder the cycloaddition of the furan moiety to DMAD. The formation of type C adduct (**4c**) under these reaction conditions (120 °C, 6 h) was of interest since 7-oxanorbornadiene moiety of type B adduct (**3a**) did not undergo the retro Diels-Alder reaction to afford type C adduct (**4a**) even under more drastic conditions (210 °C for 3.5 h and then at 240 °C for 2 h. Recovery of **3a** was 96%), and the tandem adduct (**3c**) did not occur (150 °C for 2 h, 180 °C for 2 h, and 200 °C for 2h). When type A adduct (**2c**) was treated with DMAD (1.5 equiv.) in benzene at 120 °C for 6 h (sealed tube), type C adduct (**4c**) (21%) and type B (**3c**) (36%) were obtained. The formation of **4c** is thus considered to occur as follows; first, two molecules of type A adduct (**2c**) undergo the intermolecular Diels-Alder reaction to afford a cyclic dimer, which is converted to a linear dimer, and then underwent retro Diels-Alder reaction to give type C adduct (**4c**) (Scheme 2). The reaction of nitrofuransulfolene (**1d**) with DMAD at 120° C for 24 h was complex and only one isolated product was a dimer (**5d**) (14%) (Entry 3), indicating the cycloaddition of the nitrofuran moiety of **1d** to DMAD to possibly occur. The carbon framework of **5d** was confirmed based on its ^{13}C nmr spectrum; four carbonyl carbons (δ 169.9, 167.4, 167.3 and 161.2), ten quaternary carbons (δ 161.1, 150.9, 149.5, 149.4, 142.7, 140.6, 132.6, 131.1, 122.6 and 121.8), two methine carbons (δ 147.6 and 81.2), four methylene carbons (δ 53.2, 53.1, 52.6 and 50.9), and four methyl carbons (δ 27.5, 27.3, 26.8 and 26.3). Its ^{1}H nmr spectrum showed one aromatic proton as a singlet at δ 8.08, the bridgehead proton as a singlet at δ 5.97, as well as peaks for the remaining twelve methyl protons and eight methylene ones.

Scheme 2



2; X=Ac, NO_2
E=COOMe

5

4

With dimethyl maleate as a dienophile, bromofuransulfolene (**1b**) reacted at 120 °C for 12 h to give only two isomers of type A adduct, *endo*- and *exo*-**6b**, in 53% total yield (Entry 5). This yield was three fifths that of a similar reaction of non-substituted **1a** at 120 °C for 12 h; two isomer of type B adduct (**7a**) (*endo* 51%, *exo* 10%) and two isomers of type A adduct (**6a**) (*endo* 11%, *exo* 18%). Acetylfuransulfolene (**1c**) was found to be almost inert under the same conditions (recovery of **1c** was 70%) and gave **6c** in 17% yield (Entry 6). In the case of nitro compound (**1d**), its reaction with dimethyl maleate under the same conditions was complex and *endo*-**9c** (10%) was only the isolated product, indicating the possible cycloaddition of nitrofuran ring of **1d** to the dienophile (Entry 7).

The cycloaddition of acetyl compound (**1c**) to dimethyl fumarate at 120 °C for 20 h did not proceed smoothly (recovery of **1c** was 70%), and type A adduct (**6c**) and type C adduct (**8c**) were formed in 22% total yield (Entry 9). In the case of non-substituted **1a**, total yields of the products of a similar reaction (120 °C, 4 h) were 89%, and the adduct (**8a**) was not formed. As for the formation of acetyl-substituted type C adduct (**8c**), we presumed a direct cycloaddition of dimethyl fumarate to the 3-sulfolene moiety of **1c** was considered to occur since the reaction of **6c** with this dienophile (120 °C for 2 h and then 150 °C for 2 h) led to the recovery of **6c** in

90% yield, showing **8c** not to be a product of retro Diels-Alder reaction of type B adduct (**7c**). The reaction of bromofuransulfolene (**1b**) was also complex and afforded two isomers of type A (**6b**) and type C (**8b**) in 31% total yield (Entry 8). Nitro-substituted type C adduct (**8d**) was obtained as only the isolated product in 11% yield following the 24-hours treatment of **1d** with dimethyl fumarate (Entry 10). The configuration of all cycloadducts thus obtained could be readily determined from their ^{1}H nmr spectra. The bridgehead protons of *exo*-isomers of types A and B adducts thus appeared as singlets in the reasonable region, and those of *endo*-ones as doublets.

REFERENCES AND NOTE

1. a) T. Suzuki, K. Kubomura, H. Fuchii, and H. Takayama, *J. Chem. Soc., Chem. Commun.*, **1991**,1687. b) T. Suzuki, K. Kubomura, and H. Takayama, *Chem. Pharm. Bull.*, 1991, **39**, 2164. c) K. Ando, C. Hatano, N. Akadegawa, A. Shigihara, and H. Takayama, *J. Chem. Soc., Chem. Commun.*, **1992**, 870.
2. 2,8-Dibromide was obtained in 14% yield together with the recovery of **1a** in 7% yield. The bromination of **1a** with NBS at 100 °C in benzene gave **1b** (24%) and the dibromide (42%) together with the recovery of **1a** in 17% yield.
3. Acetic *p*-toluenesulfonic anhydride was prepared from acetyl chloride and silver *p*-toluenesulfonate in MeCN at 130 °C for 1.5 h.
4. The best yield of **1d** was obtained when **1a** was treated with nitronium triflate at -40 °C for 1.5 h. When the reaction temperature was more high than -40 °C, the yield of **1a** was low. Nitration of **1a** with NO_2BF_4 in ether at 0 °C was complex and did not afford **1d**.
5. *p*-Methoxyphenyl(trimethyl)tin was obtained by $Pd(PPh_3)_4$ catalyzed reaction of *p*-iodoanisole and hexa methylditin (2 equiv.) in toluene at 115 °C for 1.5 h, and was used without more purification.
6. **1b**: ^{1}HNmr ($CDCl_3$/TMS), δ 7.48 (1H, t, *J*=1.53 Hz), 4.21 (2H, d, *J*=1.53 Hz), 4.06 (2H, s); ms (m/z), 238, 236, 174, 172; Hrms, calcd for $C_6H_5O_3BrS$; M^+, 235.9142; found: m/z 235.9165. **1c**: ^{1}HNmr ($CDCl_3$/TMS), δ 7.53 (1H, t, *J*=1.53 Hz), 4.38 (2H, s), 4.18 (2H, d, *J*=1.53 Hz), 2.52 (3H, s). ir ($CHCl_3$);1680, 1330, 1130, 928 cm^{-1}; ms (m/z), 200 (M^+), 136, 121; Hrms, calcd for $C_8H_8O_4S$; M^+, 200.0143; found: m/z 200.0140. **1d**: ^{1}HNmr ($CDCl_3$/TMS), δ 5.75 (1H, t, *J*=1.52 Hz), 4.50 (2H, s), 4.27 (2H, d, *J*=1.52 Hz); ir ($CHCl_3$), 1530, 1370, 1345, 1135, 1010, 840 cm^{-1}; ms (m/z), 203 (M^+), 139; Hrms, calcd for $C_6H_5O_4NS$; M^+, 202.9866; found: m/z 202.9866. **1e**: ^{1} HNmr ($CDCl_3$/TMS); δ 7.47 (2H, d, *J*=9.00 Hz), 7.42 (1H, t, *J*=1.60 Hz), 6.97 (2H, d, *J*=9.00 Hz), 4.33 (2H, s), 4.19 (2H, d, *J*=1.60 Hz), 3.85 (3H, s); ms (m/z), 264 (M^+), 200; Hrms, calcd for $C_{13}H_{12}O_4S$; M^+, 264.0456; found: m/z 264.0457.
7. S. P. Forsey, D. Rajapaksa, N. J. Taylor, and R. Rodrigo, *J. Org. Chem.*, 1989, **54**, 4280.
8. a) M. G. van Campen and J. R. Johnson, *J. Am. Chem. Soc.*, 1938, **55**, 430. b) W. Hertz, *ibid.*, 1945, **67**, 1854. c) A. P. Dunlop, *Ind. Eng. Chem.*, 1948, **40**, 204.

Received, 2nd November, 1992