A NOVEL APPROACH TO FUNCTIONALIZED POLICYCLIC SYSTEMS; SYNTHESIS OF TETRACYCLIC COMPOUNDS BY SEQUENTIAL DIELS-ALDER REACTIONS OF 2-ACYLATED 4*H*,6*H*-THIENO[3,4-*c*]FURAN 5,5-DIOXIDE

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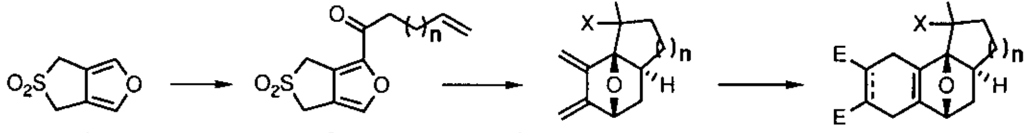
Abstract-----The 7-oxa-2,3-dimethylenenorbornene derivative (**3**), synthesized previously from 4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxide (**1**) through its 2-acylated derivative (**2**), reacted with a variety of dienophiles to give the adducts (**4**), the functionalized tetracyclic compounds, in good to excellent yield.

A novel building block, 4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxide (**1**), is potentially useful for construction of polycyclic ring systems since both of the furan and the sulfolene moieties of **1** can undergo not only the Diels-Alder reaction but also alkylation and/or acylation. Thus we have shown that **1** indeed reacts with a variety of dienophiles[1] and alkylating agents.[2] Furthermore, acylation of **1** readily took place to give 2-acylated derivative (**2**),[3] which, followed by intramolecular Diels-Alder reaction, stereoselectively afforded tricyclic compound (**3**) in good yield.[4] The adduct (**3**) should be of great synthetic utility because it has three asymmetric centers with known relative stereochemistry and a 1,3-diene which could further undergo cycloaddition to form an extra ring, namely, synthesis of functionalized tetracyclic compound (**4**). We therefore have investigated the Diels-Alder reaction of **3** with a variety of dienophiles and reported herein is the results obtained.



1 **2** **3** **4**

3 a, n=1, X,X'=$S(CH_2)_2S$
b, n=2, X,X'=$S(CH_2)_2S$
c, n=2, X,X'=$O(CH_2)_3O$
d, n=1, X,X'=CN,OTMS
e, n=2, X,X'=CN,OTMS

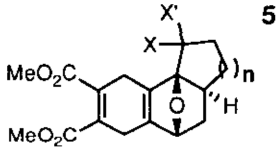
Table I Reaction of the dienes (**3a**-**e**) with dienophiles

Entry	Substrate	Dienophile	Time (h)	Products (% yield, ratio)
1	**3a**	DMAD	1	**5a** (89)
2	**3b**	DMAD	1	**5b** (95)
3	**3c**	DMAD	1	**5c** (92)
4	**3d**	DMAD	1	**5d** (88)
5	**3e**	DMAD	1	**5e** (91)
6	**3b**	*N*-Phenylmaleimide	4	**6a,b** (87, 8:1)$^{b)}$
7	**3b**	Dimethyl fumarate	24	**6c,d** (84, 8:1)$^{c)}$
8	**3b**	Dimethyl maleate	24	**6e,f** (46, 5:1), **6c** (7)$^{c)}$
9	**3b**	Benzoquinone	24	**6g** (17), **7** (56)$^{b)}$
10	**3b**	1,4-Naphthoquinone	4	**6h** (45), **8** (15)$^{b)}$
11	**3b**	Methyl propiolate	24	**9a,b** (60, 3:2), **10a,b** (36, 3:2)$^{c)}$
12	**3b**	Methyl acrylate	24	**11a** (80, 1:3:3:9)$^{c)}$
13	**3b**	1-Cyanovinyl acetate	48	**11b** (53, 1:2:2:6)$^{c)}$
14	**3b**	Acrolein	0.25	**11c** (70, 2:3:4:6)$^{c)}$

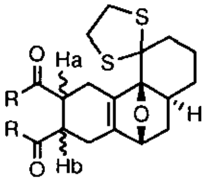
a) Reaction conditions; Entries 1-13; dienophiles (3 eq.) in toluene at reflux, Entry 14; dienophile (3eq.) and Me_2AlCl (2 eq.) in benzene at room temperature. b) The products were separated each other by chromatography. c) The adducts were obtained as an inseparable mixture and the ratio was determined by ^{1}H-nmr.

Table I summarizes the results. All the dienes (**3a**-**e**) thus far obtained[4] smoothly reacted with dimethyl acetylenedicarboxylate (DMAD) to give the corresponding adducts (**5a**-**e**),[5] respectively, in excellent yield when refluxed for 1 h in toluene (Entries 1-5). This implys that the ring size (n) nor the protective group used (x, x') does not affect the reactivity of the diene moiety in **3**. Accordingly, we used the diene (**3b**) as a representative for the following experiments. With *N*-phenylmaleimide (Entry 6), **3b** readily reacted and stereoselectively afforded the adduct (**6a**) as the major product along with the isomer (**6b**) in a ratio of 8:1. Similarly, dimethyl fumarate furnished the adducts (**6c**) and (**6d**) in high yield with the same ratio (Entry 7). The stereochemistry of these adducts was determined by ^{1}H-nmr analyses based on the data reported by Vogel and co-workers.[6] In the case of dimethyl maleate (Entry 8), however, both the yield and the selectivity were lower (45%, 5:1) and a small amount of **6c**, arose from initial isomerization of the dienophile, was obtained. The other di-substituted dienophiles, benzoquinone and 1,4-naphthoquinone, efficiently reacted again with **3b** to give the adducts (**6g**) and (**6h**), respectively, which underwent facile auto-oxidation in the reaction conditions used to produce substantial amount of the aromatized products (**7**) and (**8**), respectively (Entries 9 and 10). When methyl propiolate was used as dienophile (Entry 11), the aromatized products (**10a**) and (**10b**) were also formed, from which the regioselectivity was determined as in the ratio of 3:2 by ^{1}H-nmr analyses.[7] Moreover, all possible isomers were obtained from either methyl acrylate and 1-cyanovinyl acetate with **3b** (Entries 12 and 13). Therefore, with mono-substituted dienophiles, both the regioselectivity and the stereoselectivity of the cycloaddition were poor, nevertheless the yield of the adducts was high. Lewis acid catalyst made the reaction much faster, but improved neither the regioselectivity nor the stereoselectivity (Entry 14).[8]

Thus, the diene (**3**) was found to be highly reactive for cycloaddition and afforded the functionalized tetracyclic compound (**4**) in good to excellent yield, which further demonstrated the versatility of **1** as a building block. The ready accessibility of **4** from **1** should be applicable to synthesis of complex natural products or compounds of biological interest. Studies along this line are in progress.



5 **a**, n=1, X,X'=S(CH$_2$)$_2$S
b, n=2, X,X'=S(CH$_2$)$_2$S
c, n=2, X,X'=O(CH$_2$)$_3$O
d, n=1, X,X'=CN,OTMS
e, n=2, X,X'=CN,OTMS



6 **a**, R=N-Ph, α-Ha, α-Hb
b, R=N-Ph, β-Ha, β-Hb
c, R=OMe, α-Ha, β-Hb
d, R=OMe, β-Ha, α-Hb
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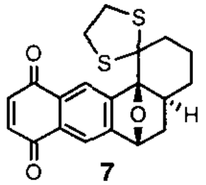
f, R=OMe, β-Ha, β-Hb
g, R= CH=CH
h, R= C$_6$H$_4$



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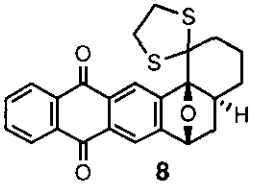

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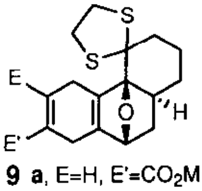
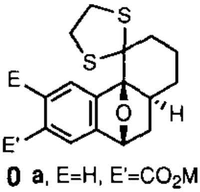
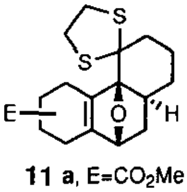


9 **a**, E=H, E'=CO$_2$Me
b, E=CO$_2$Me, E'=H



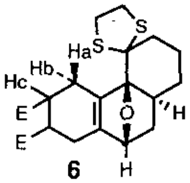
10 **a**, E=H, E'=CO$_2$Me
b, E=CO$_2$Me, E'=H



11 **a**, E=CO$_2$Me
b, E=CN, OAc
c, E=CHO

REFERENCES AND NOTES

1. a) T. Suzuki, K. Kubomura, H. Fuchii, and H. Takayama, *J. Chem. Soc., Chem. Commun.*, 1990, 1687.
   b) T. Suzuki, K. Kubomura, and H. Takayama, *Chem. Pharm. Bull.*, 1991, **39**, 2164.
2. a) K. Ando, N. Akadegawa, and H. Takayama, *J. Chem. Soc., Chem. Commun.*, 1991, 1765.
   b) K. Ando, N. Akadegawa, and H. Takayama, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2263.
3. T. Suzuki, H. Fuchii, and H. Takayama, *Heterocycles*, 1993, **35**, 57.
4. T. Hayashi, Y. Kawakami, K. Konno, and H. Takayama, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2387.
5. All new compounds were fully characterized by spectral (^{1}H-nmr, ir, ms, and high-resolution ms) and/or combustion analyses.
6. C. Maheim, P.-A. Carrupt, and P. Vogel, *Helv. Chim. Acta*, 1985, **68**, 2182. In the ^{1}H-^{1}H COSY spectra of **6**, the *exo*-allylic proton (Ha) was assignable because only this proton exhibited homoallylic coupling with the bridgehead proton in 7-oxabicyclo[2.2.1]heptene system as Vogel reported. Accordingly, taking into account of the conformation of the cyclohexene ring, the orientation of the substituent (E) could be deduced from the coupling constant of Ha-Hc. The *endo*-addition of dienophiles to the *exo*-face of 7-oxabicyclo[2.2.1]heptene system well rationalizes the stereoselectivity observed.



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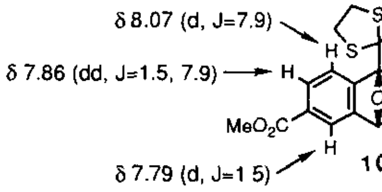
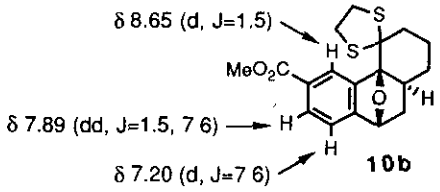
7. In the ^{1}H-nmr of a mixture of **10a** and **10b**, the signals due to aromatic protons located in the same side of the dithioketal group appeared at much lower field than the others because of the anisotropic effect of the sulfur atoms, which clearly distinguished **10a** from **10b**, hence the ratio of these compounds, namely the regioselectivity, was determined. See for a similar case; Y. Yamaguchi, H. Yamada, K. Hayakawa, and K. Kanematsu, *J. Org. Chem.*, 1987, **52**, 564.



10a



10b

8. Almost all attempts, except for this case, to react in the presence of Lewis acid catalysis resulted in exclusive formation of an unidentified product arising from the diene.

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