REGIOSELECTIVE ALKYLATION OF 5-SUBSTITUTED BENZOSULFOLENES. SOME COMMENTS FOR ITS REGIOSELECTIVITY

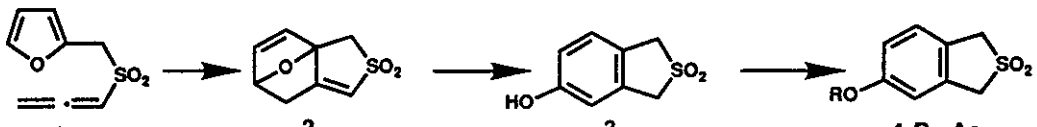
Ken Kanematsu,*[a] Isao Kinoyama,[a] Hitomi Sato,[a] Eiji Osawa,*[b] Ok-Ja Cha,[b] and Toshiyuki Hata[b]

[a]*Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences, Kyushu University, 62, Maidashi, Higashi-ku, Fukuoka 812, Japan and* [b]*Department of Knowledge-Based Information Engineering, Toyohashi University of Technology, Tempaku-cho, Toyohashi 441, Japan*

Abstract - Direct alkylation of the 5-substituted benzosulfolenes gave exclusively 3-alkylated 5-substituted benzosulfolenes. The regioselectivity was discussed in terms of the frontier molecular orbital theory.

Benzosulfolenes (1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides) are key precursors of *o*-quinodimethanes (*o*-QDM), which are very useful synthetic key intermediates[1] for many natural products such as steroids and lignans. Generally, the preparations of benzosulfolene as employed by Charlton[1] and Durst[2] have involved the reversible trapping of the *o*-QDM by sulfur dioxide of benzosulfolene. Previously, we have developed the Furan Ring Transfer (FRT) reaction: a facile method for the construction of fused furans and synthetically useful isobenzofurans.[3] Recently, we have also described the intramolecular Diels-Alder reaction of 2-furfuryl allenyl sulfone leading to one-pot synthesis of 5-hydroxybenzosulfolene (**3**)[4] as shown in Scheme I. Lately, Linde[5] has prepared benzo[*c*]thiophene *via* the intramolecular cycloaddition of 2-furfuryl allenyl sulfide in an analogue of the FRT reaction. Herein we wish to report the undisclosed alkylation of 5-substituted benzosulfolenes.

Scheme I



1 **2** **3** **4 R= Ac** **5 R= Me**

Direct methylation (MeI, KOH/DMSO, room temperature or MeI, LHMDS/THF-HMPA, -78 °C) of the 5-substituted benzosulfolenes (**4**) - (**7**) gave 3-methyl-5-substituted benzosulfolenes (**8**) - (**11**) in good yields (Scheme II). The structures of compounds (**8**) - (**11**) were assigned by referring to the nuclear Overhauser effect 2D-NMR (NOESY) spectrum. For example, an NOE for compound (**9**) was observed between the C4-H signal at δ 6.82 ppm and the methyl signal at δ 1.64 ppm indicating that the methyl group was located on C-3.

Scheme II

4 R= Ac
5 R= Me
6 R= Ms
7 R= Ts

8 R= Ac (65%)
9 R= Me (78%)
10 R= Ms (70%)
11 R= Ts (68%)

Table I. Heats of Formations, HOMO Energies and Dipole Moments of 5-Substituted Benzosulfolenes (A), Its C-3 Carbanion (B) and C-1 Carbanion (C)

X		ΔH_f kcal/mol	$\Delta\Delta H_f$[a] kcal/mol	HOMO eV	dipole moment Debye
$N(CH_3)_2$	A	-44.72		-8.772	5.92
	B	-77.12	-1.14	-3.444	8.56
	C	-75.98		-3.318	8.84
OCH_3	A	-79.16		-9.440	5.79
	B	-112.73	-0.24	-3.482	7.82
	C	-112.49		-3.474	6.82
$OCOCH_3$	A	-120.24		-9.628	5.59
	B	-157.43	0.25	-3.575	9.92
	C	-157.68		-3.560	10.26
CH_3	A	-50.55		-9.733	5.23
	B	-82.66	0.19	-3.374	5.94
	C	-82.85		-3.356	5.96
CF_3	A	-198.27		-10.542	2.35
	B	-240.08	3.60	-3.838	7.28
	C	-243.68		-4.017	6.65
$COCH_3$	A	-82.45		-10.198	4.99
	B	-119.29	4.73	-3.632	7.80
	C	-124.02		-3.869	5.91
CN	A	-4.98		-10.287	2.36
	B	-46.66	3.48	-3.854	3.84
	C	-50.14		-3.983	1.45
NO_2	A	-48.37		-10.788	2.55
	B	-94.19	8.82	-4.059	4.03
	C	-103.01		-4.508	0.82

[a] $\Delta\Delta H_f = \Delta H_f$ of C-3 carbanion - ΔH_f of C-1 carbanion in kcal /mol.

Interestingly with the idea of favoring selective deprotonation at C-1 by means of a strong electron-accepting substituent in the C-5 position, 5-cyanobenzosulfolene underwent regioselective deprotonation and alkylation with 6-bromo-1-hexene.[6] This contrasting selectivity observed in the direct methylation of 5-substituted benzosulfolenes (exclusive reaction at C-3 for 5-methoxy and 5-acyloxy derivatives and C-1 for 5-cyano derivative) is an interesting example of the remote substituent effect. Thus, we attempted to rationalize the selectivity using semi-empirical molecular orbital calculations (heats of formations, HOMO energies, and dipole moments of 5-substituted benzosulfolenes) (MOPAC/PM3) [7,8] as shown in Table I. Table II shows the HOMO coefficients in the mono- and dianions of 5-substituted benzosulfolenes. However, the results are not clear, since the 5-cyano group produces significant preference of C-1 to C-3 in the electrophilic addition to its monoanion with regards to the HOMO energy level E (1-anion 0.13 eV lower than 3-anion, see Table II) and relative stability of anionic species (heat of formation of 1-anion 3.5 kcal/mol lower than that of 3-anion, see Table I). On the contrary, the HOMO coefficients at C-1 and C-3 indicate some preference at C-3 to C-1 not only for monoanions but also for a hypothetical 1,3-dianion (see Table II). As for the 5-methoxy group, all indications on monoanions point to significantly small preference of C-3 to C-1 as the reaction site, but the calculated preference is not large enough to warrent the observed large selectivity. Accordingly, Oppolzer's explanation[6] on the regioselectivity in the 5-cyano derivatives does not apply to the 5-methoxy derivative either. The high regioselectivity caused by the 5-substituents remains unanswered at present stage. The actual picture of these phenomena is much complex than our simple expectations.

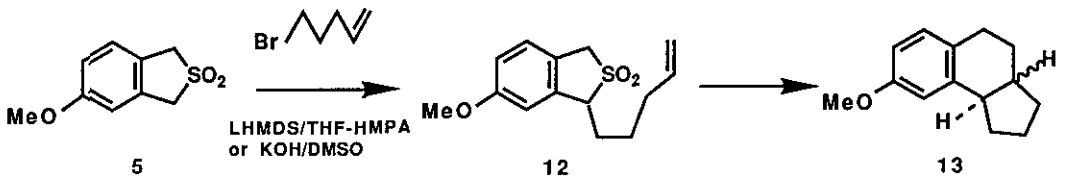
Table II. HOMO Coefficients in the Mono- and Dianions of 5-Substituted Benzosulfolenes Calculated by PM3

X	coefficient of carbanions[a]			
	C-1	C-3	C-1,3	
			C-1	C-3
OCH_3	0.66989	0.68153	0.4888	0.483
CN	*0.63641*	*0.68281*	*0.411*	*0.542*

[a] Coefficient of atomic orbital perpendicular to the molecular plane.

It is pointed out that the synthetic methodology provides an efficient means for gaining access to isomeric multiply fused ring systems through double intramolecular thermal Diels-Alder reactions of 2-furfuryl propynyl sulfone derivatives. Treatment of **5** with 5-bromo-1-pentene in the presence of base (LHMDS/THF-HMPA or KOH/DMSO) furnished exclusively 5-methoxy-3-(4-pentenyl)benzosulfolene **(12)** in 56% yield. Thermolysis of **12** in refluxing *p*-cymene at 230 °C for 4 h in a sealed tube gave 8-methoxy-2, 3, 3a, 4, 5, 9*b*-hexahydro-1*H*-benzo[*c*]indene **(13)** (3:1 *trans/cis*)[9] in 68% yield (Scheme III).

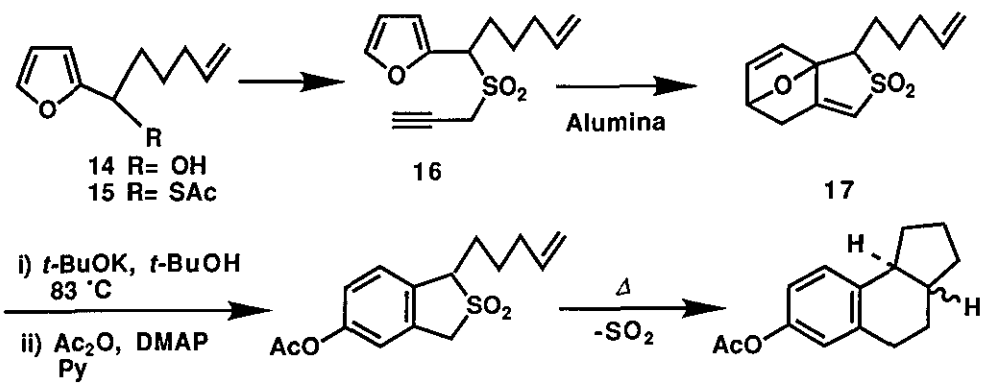
Scheme III



5 12 13

On the other hand, the key product (**16**) was prepared from Grignard reaction of 4-pentenylmagnesium bromide with furfural followed by thioacetylation (the Rapoport's method),[10] hydrolysis, propynylation, and oxidation. Successive alumina-catalyzed cyclization of **16** followed by ring-opening, and acylation afforded 5-acetoxy-1-(4-pentenyl)benzosulfolene (**18**). Thermolysis of **18** gave 7-acetoxy-2, 3, 3a, 4, 5, 9*b*-hexahydro-1*H*-benzo-[*c*]indene (**19**) (3:1 *trans/cis*)[9] in 82% yield (Scheme IV).

Scheme IV



REFERENCES AND NOTES

1. J. L. Charlton and M. M. Alauddin, *Tetrahedron*, 1987, **43**, 2873.
2. (a) T. Durst, E. C. Kozma, and J. L. Charlton, *J. Org. Chem.*, 1985, **50**, 4829.
   (b) J. L. Charlton, G. L. Plourde, K. Koh, and A. S. Secco, *Can. J. Chem.*, 1990, **68**, 2022.
3. Y. Yamaguchi, N. Tatsuta, K. Hayakawa, and K. Kanematsu, *J. Chem. Soc., Chem. Commun.*, 1989, 470.
4. K. Kanematsu and I. Kinoyama, *J. Chem. Soc., Chem. Commun.*, 1992, 735.
5. H. F. G. Linde, N. Krämer, and A. Flohr, *Arch. Pharm.*, 1988, **321**, 403.
6. W. Oppolzer and D. A. Roberts, *Helv. Chim. Acta*, 1980, **63**, 1703.
7. J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 221.
8. J. J. P. Stewart, JCPE P44, MOPAC version 6.
9. K.C. Nicolaou, W.E. Barnette, and P. Ma, J. Org. Chem., 1980, **45**, 1463.
10. R. B. Barbel and H. Rapoport, *J. Med. Chem.*, 1975, **18**, 1074.

Received, 16th September, 1993