Stereochemistry of the α-Sulfinyl Phenylmethyl Carbanion. Reevaluation of the Configuration

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Methyl phenylmethyl sulfoxide and *tert*-butyl phenylmethyl sulfoxide were subjected to H-D exchange and methylation in tetrahydrofuran and water or methanol. The stereochemistry of electrophilic attack depends on the reaction conditions and on the electrophile. Previous results reported in the literature have been reevaluated and reinterpreted. It is concluded that the HSAB principle can be applied to the course of the reaction.

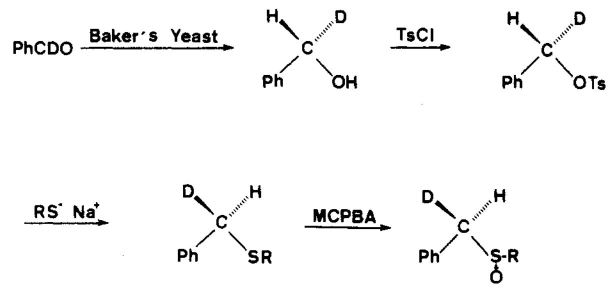
The stereochemistry of the α-sulfinyl carbanion has been a subject of extensive controversy. The reactive hydrogen in methyl phenylmethyl sulfoxide changes with a change in the reaction medium; the benzylic *pro-R* hydrogen exchanges with deuterium when the (*S*)-sulfoxide is dissolved in alkaline deuterium oxide or in deuteriated methanol containing sodium methoxide,[1,2] whereas deuterium is incorporated into the benzylic *pro-S* position when the sulfoxide is treated with BuLi/D_2O in tetrahydrofuran (THF).[3] Methylation of the same carbanion in THF with methyl iodide, however, takes place on the *pro-R* position.[3] Durst and his co-workers also reported that the deuteriation and methylation of (*R*)-*tert*-butyl phenylmethyl sulfoxide in THF occur in the *pro-R* and *pro-S* positions, respectively.[3] It should be noted that the *R*,*S* notation appears different in methyl and *tert*-butyl phenylmethyl sulfoxides because of the definition. However, the configurations at the sulfur atom are the same in these sulfoxides. It has been suspected that the observation described above is the result of complex combinations of kinetic and thermodynamic acidities of the benzylic hydrogens as well as stereochemical retention or inversion associated with the electrophilic attack.

Quite recently, Iitaka and his co-workers found, based on neutron diffraction crystallography, that the absolute configuration of monodeuteriated C_R,S_R-*tert*-butyl phenylmethyl sulfoxide was erroneously assigned by Durst and his co-workers.[4] This finding has cast doubt on the configuration of the deuteriated benzyl group in the sulfoxides studied by Durst and his co-workers. Without confirmation of the configuration of the deuteriated benzyl group, no prediction of the stability/reactivity of an α-sulfinyl carbanion can be meaningful. We have therefore reexamined the configuration of the deuteriated benzyl group and reinterpreted the results reported by Durst and his co-workers.

Results

(*S*)-Benzyl alcohol-α-*d* was obtained from benzaldehyde-α-*d* by reduction with bakers' yeast.[5,6] The alcohol was tosylated and followed by methylthiolation. Since the methylthiolation proceeds with inversion of configuration,[6] this benzyl methyl sulfide has the *R* configuration at the benzylic position. Thus, oxidation of the sulfide unambiguously gave C_R,S_{rac}-methyl phenylmethyl sulfoxide, C_R,S_{rac}-1-*d*. Monodeuteriated *tert*-butyl phenylmethyl sulfoxide with *R* configuration at the benzylic position, C_R,S_{rac}-2-*d*, was also prepared by the same procedure (Scheme I).

Scheme I



R = Me : C_RS_{rac}-1-*d*

R = *tert*-Bu : C_RS_{rac}-2-*d*

The ^{1}H NMR spectrum of S_S-1 prepared according to the literature procedure[7] and contaminated by a small amount of S_{rac}-1 is shown in Figure 1a. Figure 1b shows the ^{1}H NMR spectrum of C_RS_{rac}-1-*d* contaminated by a small amount of C_{rac},S_{rac}-1-*d* prepared from racemic benzyl alcohol-α-*d*. From parts a and b of Figure 1, it is obvious that the signals from the benzylic protons in the S_S isomer appear at lower fields than those of the S_R isomer regardless of the configuration of the benzylic carbon. A large signal appears at a higher field in the upfield pair in Figure 1b, which indicates that this signal corresponds to the benzylic proton of the C_RS_R isomer and the other large signal is that from the C_RS_S isomer.[2] Consequently, the singlets in Figure 1b can be assigned to the benzylic protons in the C_RS_S, C_SS_R, C_SS_S, and C_RS_R isomers, respectively, from lower to higher field.

The carbanion from S_S-1 in THF was deuteriated at −78 °C, and the product was subjected to ^{1}H NMR spectroscopy. The spectrum is shown in Figure 1c. There is no doubt that the product is the isomer of C_SS_S configuration, in agreement with the result reported by Durst and his co-workers.[3]

The same procedure applied to the deuteriated product from S_R-2[7] revealed that this is the C_SS_R isomer, in agreement with the result from the recent crystallographic study.[4] The ^{1}H NMR spectra of 2 and 2-*d* are shown in Figure 2.

(1) Baldwin, J. E.; Hackler, R. E.; Scott, R. M. *J. Chem. Soc., Chem. Commun.* 1969, 1415-1416.
(2) Durst, T.; Fraser, R. R.; McClory, M. R.; Swingle, R. B.; Viau, R.; Wigfield, Y. Y. *Can. J. Chem.* 1970, *48*, 2148-2150.
(3) Durst, T.; Viau, R.; McClory, M. R. *J. Am. Chem. Soc.* 1971, *93*, 3077-3078.
(4) Iitaka, Y.; Itai, A.; Tomioka, N.; Kodama, Y.; Ichikawa, K.; Nishihata, K.; Nishio, M.; Izumi, M.; Doi, K. *Bull. Chem. Soc. Jpn.* 1986, *59*, 2801-2806.
(5) Streitwieser, A., Jr.; Wolfe, J. R., Jr.; Schaeffer, W. D. *Tetrahedron* 1959, *6*, 338-344.
(6) Althouse, V. E.; Feigl, D. M.; Sanderson, W. A.; Mosher, H. S. *J. Am. Chem. Soc.* 1966, *88*, 3595-3599.
(7) Axelrod, M.; Bickart, P.; Jacobus, J.; Green, M. M.; Mislow, K. *J. Am. Chem. Soc.* 1968, *90*, 4835-4842.

0022-3263/87/1952-1414$01.50/0

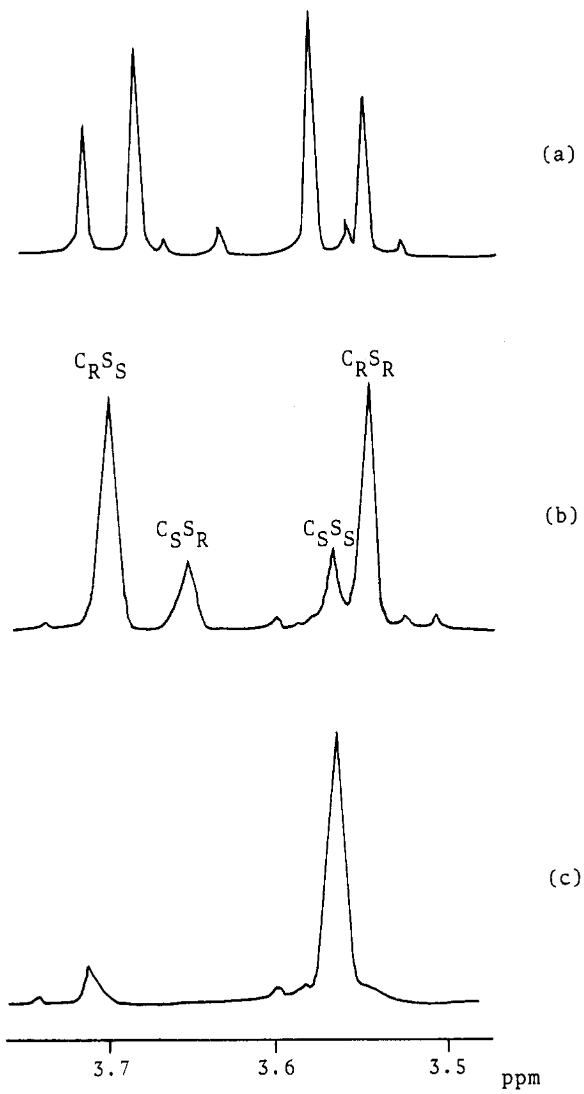
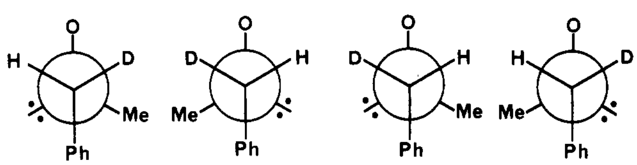


Figure 1. ^{1}H NMR spectra: (a) S_S-methyl phenylmethyl sulfoxide (**1**) contaminated by a small amount of S_{rac}-**1**; (b) C_R,S_{rac}-**1**-*d* contaminated by a small amount of C_{rac},S_{rac}-**1**-*d*; (c) S_S-**1**-*d* obtained by deuteriation of S_S-**1** in THF.



C_RS_S-1-*d* C_SS_R-1-*d* C_SS_S-1-*d* C_RS_R-1-*d*

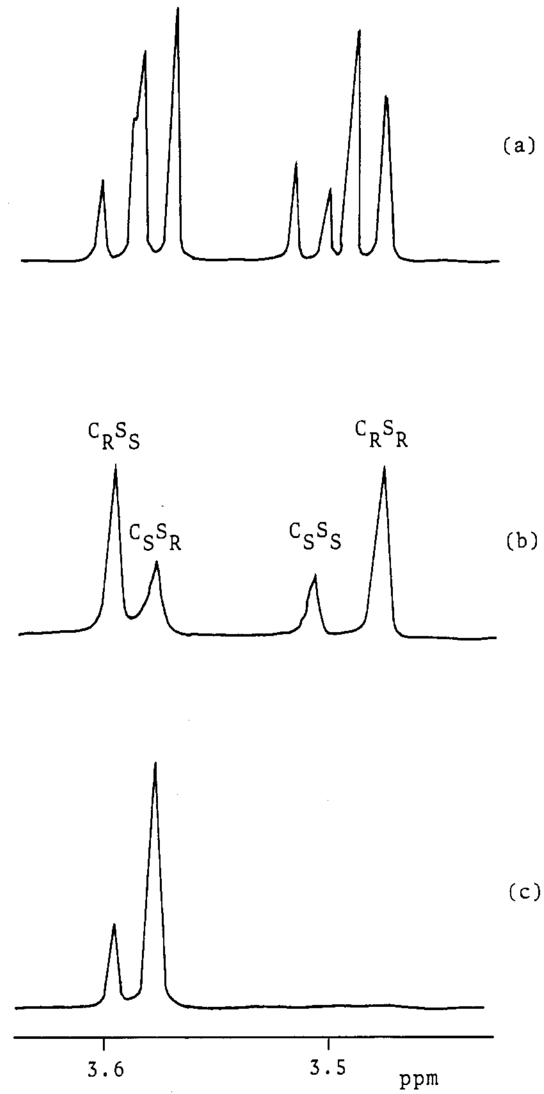
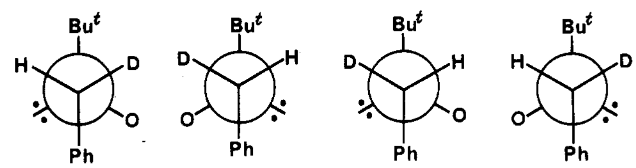
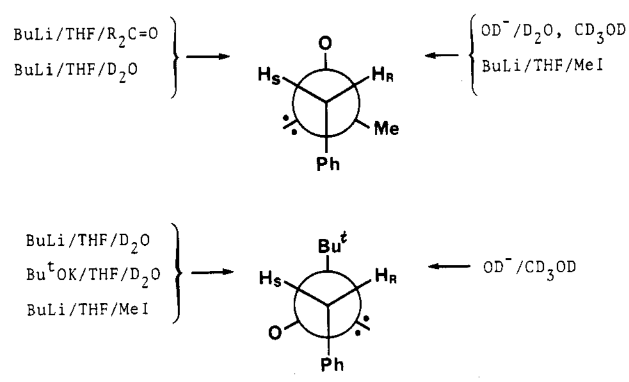


Figure 2. ^{1}H NMR spectra: (a) S_R-*tert*-butyl phenylmethyl sulfoxide (**2**) contaminated by a small amount of S_{rac}-**2**; (b) C_R,S_{rac}-**2**-*d* contaminated by a small amount of C_{rac},S_{rac}-**2**-*d*; (c) S_R-**2**-*d* obtained by deuteriation of S_R-**2** in THF.



C_RS_S-2-*d* C_SS_R-2-*d* C_SS_S-2-*d* C_RS_R-2-*d*

Scheme II

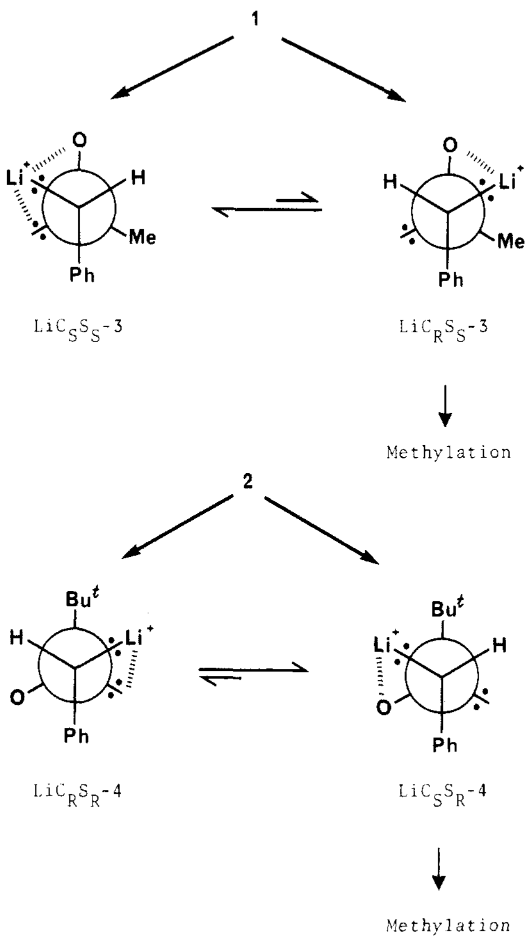


Compound S_S-**1** exchanges its benzylic *pro-R* hydrogen by the reaction in a polar protic solvent, in contrast to the exchange in THF. There is, however, no corresponding observation on **2**, and we studied the exchange reaction of S_R-**2** in methanol to obtain information on the stereochemistry of the exchange in relation to the reaction medium. The observed stereoselectivity was much smaller in **2** than in **1**, and the ratio of reactivities of *pro-R* to *pro-S* hydrogens in methanol in the presence of sodium methoxide at room temperature was 2:1 with preference for the formation of C_RS_R-**2**-*d* over C_SS_R-**2**-*d*. C_SS_R-**2**-*d*. Here again, the stereochemistry of the exchange reaction was affected by the reaction medium.

Discussion

The present results together with those reported previously are summarized in Scheme II. It is now obvious that deuteriation and methylation of **1** in THF occur with opposite stereospecificity, whereas the corresponding re-

Scheme III



actions of **2** in THF proceed with the same stereospecificity. Thus, methylation does not necessarily occur with inversion of configuration.

The stereochemistry of the reaction products depends on the α-sulfinyl carbanion by three factors: (i) kinetic acidity, which controls the stereochemistry of the carbanion initially formed; (ii) thermodynamic acidity, which defines the stereochemistry or the conformation of the intermediate carbanion; (iii) reactivity of the carbanion, which may be important to control the stereochemistry of the products. It should also be noted that the carbanion, as well as the base used to form it, is not *free* but is always accompanied by a countercation. Thus, the stereochemistry of the products does not necessarily reflect the stable conformation of the *free* carbanion.

For the present reaction system, the contribution of kinetic acidity can be neglected because the carbanion in THF has enough time to reorganize into its most stable conformation before it reacts with an electrophile.

Although measurement of the nuclear Overhauser effect in **1** did not indicate a frozen conformation even at –50 °C, it is expected from steric bulk that the methyl group is gauche to the phenyl group in a stable conformation of **1** in a nonpolar solution, especially when the sulfinyl oxygen coordinates with a cationic portion of a polar molecule such as a lithium salt or water. This expectation is partly supported by the result of an ORD measurement.[8] On the other hand, measurements of circular dichromism[9] and of the ^{1}H NMR lanthanide shift[10] indicate that **2** in solution has the conformation in which the *tert*-butyl group and the sulfinyl oxygen are anti and gauche to the phenyl group, respectively (Scheme III).[9]

In THF, the countercation of a base employed to abstract a proton from the sulfoxide would initially be trapped by the sulfinyl oxygen. Therefore, the H_S in S_R-**2** is more reactive than the H_R, and the carbanion formed on that side is more stable than the other one. The H_R and H_S in S_S-**1** are similar in reactivity and stability with respect to distance from the sulfinyl oxygen. However, the thermodynamic stability is larger on the H_S side because the countercation can be coordinated by both the oxygen and sulfur lone pairs. On the other hand, the abstraction of a hydrogen would be easier on the H_R side because the electrostatic repulsion between the developing negative charge on the H_R side and the sulfur lone pair is less than that on the H_S side.

Consequently, the (lithiated) α-sulfinyl carbanions produced from S_S-**1** and S_R-**2** may have conformations C_SS_S-**3** and C_SS_R-**4**, respectively. Water (deuterium oxide) comes from the lithiated side of the carbanions because its polarization causes it to interact initially with the countercation. However, methyl iodide is a nonpolar substrate and prefers to react on the more nucleophilic side, which is anti to the sulfur lone pair. Thus, the sulfur lone pair can exert an α-effect to make the anti lone pair more polarizable.[11]

In other words, the *si* and *re* faces of S_S-**3** are hard and soft reaction centers, respectively, and hard reagents such as proton and carbonyl compounds[3,12,13] react on the *si* face, whereas a soft reagent such as methyl iodide reacts on the *re* face. Since S_R-**4** has both hard and soft reaction centers on the same *si* face, both hard and soft reagents react on this same face.

The situation in a polar solvent is somewhat different from that in THF. A base employed to abstract a proton from the sulfoxide is not tightly paired with a countercation or attracted by the sulfinyl oxygen. Rather, the anionic base tends to keep away from the anionic face of the sulfoxide. Thus, H_R in both S_S-**1** and S_R-**2** is the reacting hydrogen in a polar solvent. The difference in anionic character of *re* and *si* faces is smaller in **2** than in **1**, and the selectivity is much higher for **1** than for **2**. This result reflects kinetic acidity in a polar solvent, because the carbanion formed in a polar solvent can react with an electrophile before it reorganizes into the most stable conformation.

It is also possible that the conformation of **1** in a polar solvent is different from that in a nonpolar solvent. The ORD spectrum of **1** changes with a change in the polarity of the solvent, and Folli and his co-workers have proposed that **1** has a **2**-type conformation in polar solvents.[8] In addition, the chemical shifts of the benzylic *pro-R* and *pro-S* hydrogens in the ^{1}H NMR spectrum of **1** are different in polar and nonpolar solvents.[2]

The above discussion is based on the assumption that the benzilic carbanion is sp^3 hybridized. However, the same arguments are valid by assuming an sp^2-hybridized carbanion, provided the coordination of the countercation is asymmetric or distorted to some extent by neighboring dipoles. We prefer to propose that the benzilic carbanion is sp^2 hybridized because the phenyl group adjacent to the

(8) Folli, U.; Montanari, F.; Torre, G. *Tetrahedron Lett.* **1966**, 5037–5044.
(9) Kodama, Y.; Nishihata, K.; Nishio, M. Iitaka, Y. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1490–1495.
(10) Kodama, Y.; Nishihata, K.; Nishio, M. *Tetrahedron Lett.* **1977**, 2105–2108. It should be noted that a wrong conclusion was deduced in this paper based on the erroneous assignment of *pro-R* and *pro-S* benzylic hydrogens.
(11) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16–24.
(12) Nishihata, K.; Nishio, M. *Tetrahedron Lett.* **1976**, 1695–1698.
(13) Nishihata, K. Ph.D. Thesis, Tokyo University, 1975.

carbanionic center would stabilize the negative charge.[14]

We sought to explain the discrepancy in the configuration of **2**-*d*, oxidizing the deuteriated sulfoxide (Figure 2c) ($[\alpha]^{24}{}_D$ +131.35°) to the corresponding sulfone. The deuteriated sulfone thus obtained showed a negative rotation (−0.273°) in contrast to the positive rotation (+0.6°) reported by Durst and his co-workers.[3] Since the starting S_R-**2** has a large positive rotation (+167°),[3] it seems possible that the contamination of the product sulfone with this sulfoxide led Durst and his co-workers to misassign the steric course of the reaction.

Experimental Section

Melting points were not corrected. ^{1}H NMR spectra were recorded at 400 MHz on a JEOL GX-400 Fourier transform NMR spectrometer. The optical activity was measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed with a Yanako MT-3 elemental analyzer.

Materials. S_S-Methyl phenylmethyl sulfoxide (S_S-**1**) and S_R-*tert*-butyl phenylmethyl sulfoxide (S_R-**2**) were prepared by Drs. Nishio and Nishioka of Meiji Seika Kaisha, Ltd., according to literature procedures.[7,15] (*S*)-(+)-α-Deuteriobenzyl alcohol obtained as described in a previous paper[5,6] was converted into C_R,S_{rac}-**1**-*d* and C_R,S_{rac}-**2**-*d* according to the literature procedure.[1]

Deuteriation of Sulfoxide. Into a 200-mL flask were placed 3.1 g (20.1 mmol) of S_S-**1** [$[\alpha]^{24}{}_D$ +100° (*c* 1.30, EtOH); mp 56–58 °C] and 70 mL of THF under an argon atmosphere. The mixture was cooled to −78 °C and stirred. A solution of *n*-butyllithium in hexane (13 mL, 20.3 mmol) was added to this mixture through a syringe. The mixture was kept at −78 °C for an additional 1 h and quenched with 4 mL of deuterium oxide. The reaction mixture was further stirred without cooling. Then, 20 mL of 2 N HCl was added, and the solvent was evaporated under reduced pressure. The residue was extracted with dichloromethane, and the organic layer was washed with water and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was chromatographed on a column of silica gel with EtOAc/EtOH (9/1) as eluent to afford 1.4 g (45.2%) of S_S-**1**-*d* (mp 56–58 °C).

Oxidation of Sulfoxide. C_R,S_{rac}-**1**-*d* (mp 59–60 °C) was oxidized with *m*-chloroperbenzoic acid in dichloromethane into the corresponding sulfone [$[\alpha]^{24}{}_D$ +0.885° (*c* 0.565, $CHCl_3$); mp 123–125 °C], and the sign of optical rotation was compared with that of sulfone obtained from sulfoxide S_S-**1**-*d* [$[\alpha]^{24}{}_D$ −0.561° (*c* 0.535, $CHCl_3$); mp 123–124 °C].

S_R-**2** [$[\alpha]^{24}{}_D$ +140° (*c* 1.10, EtOH); mp 72–73 °C] was deuteriated similarly to give S_R-**2**-*d*, which was further oxidized into *tert*-butyl phenylmethylsulfone [$[\alpha]^{24}{}_D$ −0.273° (*c* 2.56, EtOH); mp 122–123 °C] by *m*-chloroperbenzoic acid in dichloromethane at 0 °C, and the sign of optical rotation of this sulfone was compared with that of the sulfone obtained from C_R,S_{rac}-**2**-*d* [$[\alpha]^{24}{}_D$ +0.419 (*c* 4.53, EtOH); mp 124–125 °C].

Thus, it was confirmed, from the viewpoint of optical rotation, that the configurations at the benzylic carbons of both **1** and **2** are *S*, in agreement with the results from ^{1}H NMR spectroscopy.

Measurement of Nuclear Overhauser Effect. A sulfoxide, **1** or **2** (10 mg), was dissolved in 500 μL of $CDCl_3$, and the solution was subjected to ^{1}H NMR spectroscopy at room temperature or at −50 °C with tetramethylsilane as an internal standard.

The irradiation of the signal from the methyl group caused no appreciable difference in the increase in the intensity of the signal between the benzylic *pro-R* and *pro-S* protons in **1** and **2**.

(14) Lett, R.; Chassaing, G.; Marquet, A. *J. Organomet. Chem.* **1976**, *111*, C17–C20.

(15) We thank them for the gift.

Dipolar Cycloaddition Reactions of (Phenylsulfonyl)alkynes and (Phenylsulfonyl)propadiene with *C*,*N*-Diphenylnitrone

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The reaction of the title nitrone with (phenylsulfonyl)alkynes **1a**,**b** results in 3-acylindoles **6a**,**b** via unstable 4-isoxazoline cycloadducts which evolve by fission of the N–O bond and subsequent reclosure onto the ortho position of the *N*-phenyl substituent. Under the same conditions, the title nitrone reacts with (phenylsulfonyl)propadiene (**10**) to give the isomeric benzazepinone **12** and pyrrolidone **11**, both of which are presumably formed from a common, transient cycloadduct. Compound **12** changes readily through a novel pathway leading to the indole derivative **14**.

Extensive interest has been shown in Diels–Alder[1,2] and 1,3-dipolar[3] cycloadditions to ethylenic sulfones in view of the activating and (potentially) regiocontrolling effect of the sulfonyl group as well as of the synthetic usefulness of the resulting adducts through alkylation and/or desulfonylation. However, minor investigation has been done on the dienophilic[1,4] and dipolarophilic[5–8] reactivity of allenic and acetylenic sulfones. In previous papers,[6] we reported the reactions of (phenylsulfonyl)alkynes (**1a**,**b**) and (phenylsulfonyl)propadiene (**10**) with nitrile oxides and imines. In continuation of this line of research, we

(1) De Lucchi, O.; Modena, G. *Tetrahedron* **1984**, *40*, 2585 and references therein.

(2) Carr, R. V. C.; Williams, R. V.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4976. Kinney, W. A.; Crouse, G. D.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4986.

(3) For recent examples, see: De Benedetti, P. G.; Quartieri, S.; Rastelli, A.; De Amici, M.; De Micheli, C.; Gandolfi, R.; Gariboldi, P. *J. Chem. Soc., Perkin Trans. 2* **1982**, 95. Caramella, P.; Albini, E.; Bandiera, T.; Corsico Coda, A.; Grünanger, P.; Marinone Albini, F. *Tetrahedron* **1983**, *39*, 689. Barzaghi, M.; Beltrame, P. L.; Dalla Croce, P.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Zecchi, G. *J. Org. Chem.* **1983**, *48*, 3807. Bened, A.; Durand, R.; Pioch, D.; Geneste, P.; Guimon, C.; Guillouzo, G. P.; Declercq, J. P.; Germain, G.; Briard, P.; Rambaud, J.; Roques, R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1. Komatsu, M.; Yoshida, Y.; Uesaka, M.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1984**, *49*, 1300.

(4) Veniard, L.; Benaim, J.; Pourcelot, G.; Normant, M.-H. *C. R. Seances Acad. Sci., Ser. C* **1968**, 1092. Barbarella, C.; Cinquini, M.; Colonna, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1646. Guildford, A. J.; Turner, R. W. *J. Chem. Soc., Chem. Commun.* **1983**, 466. Hayakawa, K.; Nishiyama, H.; Kanematsu, K. *J. Org. Chem.* **1985**, *50*, 512.

(5) Guillerm, G.; L'Honoré, A.; Veniard, L.; Pourcelot, G.; Benaim, J. *Bull. Soc. Chim. Fr.* **1973**, 2739.

(6) (a) Bruché, L.; Gelmi, M. L.; Zecchi, G. *J. Org. Chem.* **1985**, *50*, 3206. (b) Dalla Croce, P.; La Rosa, C.; Zecchi, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2621.

(7) Blechert, S. *Justus Liebigs Ann. Chem.* **1985**, 673.

(8) Padwa, A.; Carter, S. P.; Chiacchio, U.; Kline, D. N. *Tetrahedron Lett.* **1986**, *27*, 2683.

0022-3263/87/1952-1417$01.50/0