Tandem Nitroaldol−Dehydration Reactions Employing the Dianion of Phenylsulfonylnitromethane[1]

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Received January 8, 2000

Reaction of phenylsulfonylnitromethane (**1**) with more than 2 molar equiv of LDA afforded the dilithium salt of phenylsulfonylnitromethane. Condensation of this dilithium salt with unbranched aldehydes occurred readily, but the initial nitroaldols dehydrated to afford unconjugated *β*,*γ*-unsaturated α-nitrosulfones in 52−88% yield. Evidence is presented that the *β*,*γ*-unsaturated α-nitrosulfones can equilibrate with the conjugated α,*β*-unsaturated α-nitrosulfones at neutral pH. The normally disfavored α,*β*-unsaturated α-nitrosulfones have been implicated in the formation of bis(α-nitrosulfones), Michael adducts of phenylsulfonylnitromethane. Three diastereomers (1*R*,2*s*,3*S*, 1*R*,2*r*,3*S*, and 1*R*,3*R*/1*S*,3*S*) have been identified for the bis(α-nitrosulfones) obtained in these reactions. In the case of acetaldehyde, condensation with the dilithium salt of phenylsulfonylnitromethane afforded only bis(α-nitrosulfones). The main product (three diastereomers) was the bis(α-nitrosulfone) derived from Michael addition of phenylsulfonylnitromethane and a minor product was tentatively identified as the bis(α-nitrosulfone) derived from dimerization. Also formed in the reaction of propanal with the dilithium salt of phenylsulfonylnitromethane was an unstable *β*-amine, the formal conjugate addition product of diisopropylamine to the α,*β*-unsaturated α-nitrosulfone. When tandem nitroaldol/dehydration reactions were carried out in the presence of thiols, the α,*β*-unsaturated α-nitrosulfones were intercepted to provide *β*-sulfides, the products of conjugate addition, in 61−83% yield.

Introduction

Arenesulfonylnitromethanes are quite acidic: Bordwell and Bartmess[2] have reported a pK_a of 5.7 for phenylsulfonylnitromethane (**1**). This, coupled with the relatively congested carbon site, causes the monoanions of arenesulfonylnitromethanes to be poor nucleophiles. In accordance with this fact, Zeilstra and Engberts have reported[3] an unsuccessful attempt to condense *p*-tolylsulfonylnitromethane with aldehydes under basic conditions,[4] although they were able to condense *p*-tolylsulfonylnitromethane with aldehydes and benzenesulfinic acid in aqueous formic acid. In contrast to the monoanions derived from arenesulfonylnitromethanes, the more nucleophilic anion derived from phenylthionitromethane has been reported[5] to add smoothly to a number of aldehydes.

Seebach et al.[6] have prepared a series of nitroalkane dianions by α,α-doubly deprotonating primary nitro compounds and have shown that these dianions undergo nitroaldol condensation with aldehydes. Simple nitroalkanes, aromatic substituted nitroalkanes, and phenylthionitromethane have been reported to undergo this interesting double deprotonation−nitroaldol sequence. Formation of the dianions was performed using a very strong base (butyllithium) and extremely cold reaction temperature (−90 °C). The questions then arise: Might the dianion of a very acidic nitro compound such as phenylsulfonylnitromethane be more readily formed and, if so, would it then undergo useful nitroaldol transformations?

Results and Discussion

Reaction of phenylsulfonylnitromethane with 2.3 molar equiv of lithium diisopropylamide (LDA) in tetrahydrofuran at −78 °C followed by sequential addition of propanal and glacial acetic acid led to the formation of the *β*,*γ*-unsaturated α-nitrosulfone **7a** in 88% yield after optimization (Scheme 1). Here the crude product was extracted into base to remove neutral side products followed by reacidification. A small amount, typically

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(1) α-Nitrosulfones. 3. For part 2, see: Wade, P. A.; Hinney, H. R.; Amin, N. V.; Vail, P. D.; Morrow, S. D.; Hardinger, S. A.; Saft, M. S. *J. Org. Chem.* **1981**, *46*, 765.

(2) Bordwell, F. G.; Bartmess, J. E. *J. Org. Chem.* **1978**, *43*, 3101.

(3) Zeilstra, J. J.; Engberts, J. B. F. N. *J. Org. Chem.* **1974**, *39*, 3215. Zeilstra, J. J. Ph.D. thesis, Verenigde Reproductie Bedrijven, Groningen, The Netherlands, 1975.

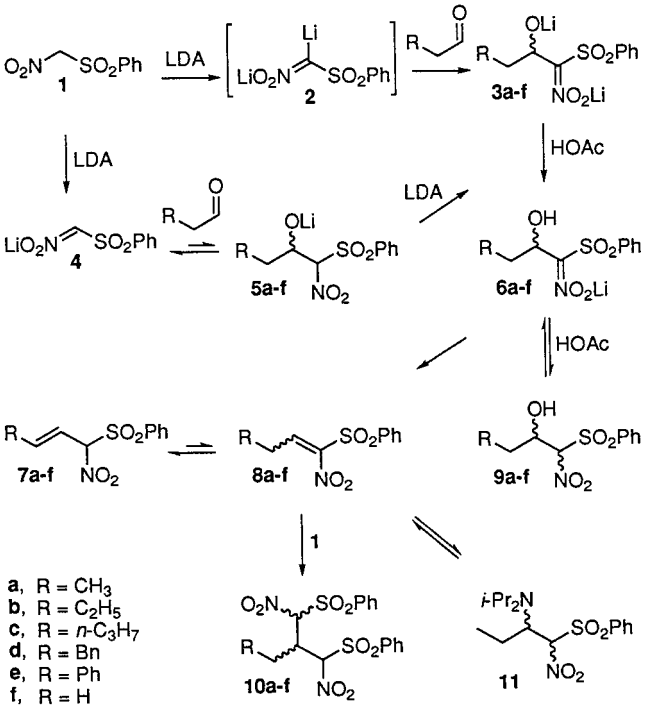
(4) Rosini et al. have recently shown that certain aldehydes possessing an α-leaving group can undergo base-promoted reaction with **1** to afford 4-hydroxy-2-isoxazoline-*N*-oxides. The 4-hydroxy-2-isoxazoline *N*-oxides were not isolated but, rather, were allowed to react further with activated olefins (e.g., chlorodimethylvinylsilane). The authors postulate an initial nitroaldol reaction of the aldehyde with **1** and subsequent intramolecular O-alkylation of the resulting nitronate to give the 4-hydroxy-2-isoxazoline-*N*-oxide: Marotta, E.; Righi, P.; Rosini, G.*Tetrahedron Lett.* **1998**, *39*, 1041; Marotta, E.; Righi, P.; Rosini, G. *Chem.-Eur. J.* **1998**, *4*, 2501.

(5) Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *J. Org. Chem.* **1986**, *51*, 1012.

(6) (a) Seebach, D.; Beck, A. K.; Triptikumar, M.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1109. (b) Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 3601. (c) For α,*β*-doubly deprotonated nitro compounds, see: Henning, R.; Lehr, F.; Seebach, D. *Helv. Chim. Acta* **1976**, *59*, 2213.

10.1021/jo0000170 CCC: $19.00
Published on Web 10/25/2000

Scheme 1



about 2−5% yield, of the bis(α-nitrosulfone) **10a** was also obtained in the crude products. On the other hand, attempts to condense lithium phenylsulfonylnitromethanate (**4**)[1] with propanal were unsuccessful: the reaction products after 24 h at room temperature consisted of a 93:3:3 mixture of starting phenylsulfonylnitromethane, alkene **7a**, and the bis(α-nitrosulfone) **10a**, respectively, following acidification. Apparently, efficient formation of **7a** requires formation of the dilithium salt **3a** prior to acidification.

Two alternative routes for the formation of **3a** were thought possible. In the first route, LDA, if sufficiently basic, could doubly deprotonate phenylsulfonylnitromethane to form the dilithium salt **2**. Condensation of the dilithium salt **2** with propanal would lead directly to **3a**, the apparent precursor to the β,γ-unsaturated α-nitrosulfone **7a**. Alternatively, LDA might only be capable of singly deprotonating phenylsulfonylnitromethane to afford the lithium salt **4**. Reaction of **4** with propanal might occur to form the lithium alkoxide **5a** in low concentration. Deprotonation of **5a** by excess LDA could then afford the dilithium salt **3a** driving condensation toward completion.

To distinguish between the two mechanistic possibilities, the stoichiometry for reaction of LDA with phenylsulfonylnitromethane was established. A THF solution of LDA containing triphenylmethane was titrated with a THF solution of phenylsulfonylnitromethane. Dissipation of the blood-red color of lithium triphenylmethide occurred after addition of only 0.5 molar equiv of phenylsulfonylnitromethane. It is therefore concluded that dilithium salt **2** was formed from reaction of excess LDA with phenylsulfonylnitromethane and that **2** must be the actual species condensing with propanal to furnish **7a**. Apparently the second pK_a of phenylsulfonylnitromethane in THF is less than 31 (i.e., the lithium salt **4** of phenylsulfonylnitromethane is a stronger acid than triphenylmethane, pK_a 31.48[7]).

Two unstable intermediates were observed in the condensation of dilithium salt **2** with propanal. The first of these was the intermediate nitroaldol **9a**. Nitroaldol **9a** (50% of the crude products) was observed, accompanied by β,γ-unsaturated α-nitrosulfone **7a**, when the reaction products were examined directly after addition of glacial acetic acid. The ^{1}H NMR signals attributed to **9a** gradually disappeared on standing for a day in contact with traces of acid, more rapidly in the presence of excess acetic acid or when warmed. Two diastereomers of the nitoaldol (60:40 ratio by ^{1}H NMR) were apparent. The low diastereioselectivity is consistent with observations made by Seebach et al.[6a] for acidification of dianions under conditions similar to those we employed, namely in the absence of HMPA or DMPU. Presumably, the first protonation of **3a** occurred preferentially at the more basic alkoxide site (pK_a = 16.48[8] for 2-propanol, a representative secondary alcohol) rather than at the less basic nitronate site (pK_a = 5.7 for **1**,[2] a representative α-nitrosulfone). A subsequent protonation of **6a** afforded the nitroaldol **9a**: here the *aci*-nitro tautomer was also possible, indeed likely, but was not observed.

With regard to dehydration, there is ample evidence that the α,β-unsaturated α-nitrosulfone **8a** was formed prior to the β,γ-unsaturated α-nitrosulfone **7a**. In all runs, **10a**, the Michael adduct of **7a** and phenylsulfonylnitromethane (**1**) was formed as a side product. The amount of bis(α-nitrosulfone) **10a** was variable, but in certain cases where substantial amounts of **1** remained, **10a** constituted more than 25% of the crude product.

A second unstable intermediate, β-amine **11** (25% of the crude product), accompanied by β,γ-unsaturated α-nitrosulfone **7a**, was obtained in certain runs when the reaction was examined directly after addition of glacial acetic acid. Here, the nitroaldol had completely dehydrated and free diisopropylamine (possibly excess LDA) had undergone conjugate addition to the intermediate α,β-unsaturated α-nitrosulfone **8a** affording the β-amine **11**, present as two diastereomers (65:35 ratio). The ^{1}H NMR signals attributed to **11** disappeared from the crude products during the usual base−acid workup and an attempt to obtain pure **11** by preparative TLC led to complete decomposition of **11**. On protracted standing in the freezer, signals attributed to **11** disappeared while signals for **10a** and phenylsulfonylnitromethane increased: presumably **11** readily eliminates diisopropylamine to afford α,β-unsaturated α-nitrosulfone **8a**, which in turn affords **7a**, phenylsufonylnitromethane, and **10a**.

An E1cb pathway for the formation of the α,β-unsaturated α-nitrosulfone has been considered, but no supporting evidence has been obtained for it. In the case of the nitroaldol **9a**, a likely pathway would involve deprotonation to **6a**, and subsequent loss of the hydroxyl group furnishing the α,β-unsaturated α-nitrosulfone **8a**. It is reasonable that, even in the presence of excess acetic acid (pK_a 4.76), the acidic **9a** could ionize to provide **6a** in sufficient concentration for dehydration. Thus, the propensity for dehydration observed here, in contrast to the studies of Seebach et al. where the nitroaldols do not readily dehydrate, is likely a consequence of the high acidity of **9a**. A similar process likely operates with the

(7) pK_a of triphenylmethane in cyclohexylamine: Streitwieser, A., Jr.; Ciuffarin, E.; Hammons, J. H. *J. Am. Chem. Soc.* **1967**, *89*, 63.

(8) pK_a of 2-propanol in alcoholic media: Reeve, W.; Erikson, C. M.; Aluotto, P. F. *Can. J. Chem.* **1979**, *57*, 2747.

Table 1. Products Obtained from Reaction of LiC(=NO2Li)SO2Ph (2) with Unbranched Aldehydes

RCH2CH=O R =	7	yield, %	10	yield, %
CH_3	**7a**	88	**10a**	2
CH_3CH_2	**7b**	77	**10b**	2
$CH_3CH_2CH_2$	**7c**	70	**10c**	1
$PhCH_2$	**7d**	52	**10d**	10
Ph	**7e**	75	**10e**	0
H	**7f**	0	**10f**	80[a]

[a] Also obtained was bis(α-nitrosulfone) **13** in 6% yield.

β-amine **11**, which is, however, somewhat more stable than the nitoaldol **9a**. Substantial reversion to propanal and phenylsulfonylnitromethane did not normally occur during acidification, although some of the starting phenylsulfonylnitromethane could always be isolated from the crude products. Under conditions optimized for formation of **7a**, the amount of remaining phenylsulfonylnitromethane was 2−5% of the product. On the other hand, immediate treatment of the crude products containing nitroaldol **9a** with aqueous sodium hydroxide followed by reacidification resulted in a substantially increased formation of starting phenylsulfonylnitromethane: rapid hydroxyl deprotonation and fragmentation of the ensuing sodium alkoxide (analogous to the lithium alkoxide **5a**) would be the cause.

The scope of the tandem nitroaldol−elimination sequence was next investigated by examining a series of aldehydes. Successful reactions to produce *β*,*γ*−unsaturated α-nitrosulfones **7b**−**e** in 52−77% yield were carried out using butanal, pentanal, 3-phenylpropanal, and phenylacetaldehyde (Table 1). The bis(α-nitrosulfones) **10b**−**d** were obtained as incompletely purified side products in yields ranging from 2 to 10%. Diphenylacetaldehyde and isobutyraldehyde failed to give the corresponding *β*,*γ*-unsaturated α-nitrosulfones: apparently nitroaldol dianion formation (or the stability of the dianion) is adversely affected by moderate steric bulk at the α-carbon atom of the aldehyde. In the case of acetaldehyde, too, none of the usual *β*,*γ*-unsaturated α-nitrosulfone was obtained: instead, the main product was the bis(α-nitrosulfone) **10f**, obtained in 80% yield.

Formation of the *β*,*γ*-unsaturated α-nitrosulfones **7a**−**e** was highly stereoselective. All products obtained were > 97% pure *E*-isomers: no trace of the *Z*-isomer was detected in any of the examples studied. The stereochemical assignment is based on ^{1}H NMR and ^{13}C NMR spectra. The 15.3−15.5 Hz coupling constants for the olefinic protons are only consistent with a 180° dihedral angle.[9]

The isolated alkene products were the nonconjugated *β*,*γ*-unsaturated α-nitrosulfones in all cases. Initially this seemed surprising, especially in light of the reported[5] formation of conjugated α,*β*-unsaturated α-nitrosulfides. Formation of the *β*,*γ*-unsaturated α-nitrosulfones can be rationalized on two counts. First, sulfones often prefer to be nonconjugated under equilibrating conditions.[10]

(9) The typical trans-coupling constant is 12−18 Hz and the typical cis-coupling constant is 6−12 Hz: Silverstein, R. M.; Webster, F. X. *Spectrometric Identification of Organic Compounds*; 6th ed.; Wiley: New York, 1998; p 212.

(10) Meagher, T. P.; Yet, L.; Hsiao, C.-N.; Shechter, H. *J. Org. Chem.* **1998**, *63*, 4181.

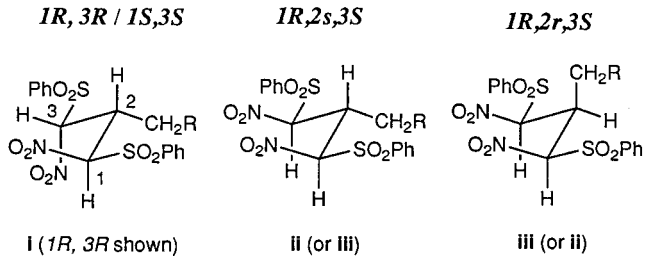
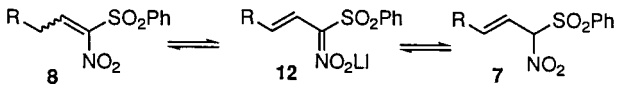


Figure 1. Bis(α-nitrosulfone) **10** diastereomers.

Second, the conjugated lithium *β*,*γ*-unsaturated nitronate **12** is present and, quite likely, the conjugated nitronic acid also. Protonation of nitronate **12** on the carbon bearing the nitro group would then afford the *β*,*γ*-unsaturated α-nitrosulfone. Indeed, the α-proton of **7a** can be readily deuterium exchanged (occasional shaking over 45 min of a $CDCl_3$ solution layered with D_2O), consistent with anion formation and reprotonation at the α-carbon.

There is evidence that the α,*β*-unsaturated α-nitrosulfones are intermediates in the formation of the *β*,*γ*-unsaturated α-nitrosulfones **7b**−**e** as in the case of **7a**. Side products **10b**−**d** derived from Michael addition of phenylsulfonylnitromethane to the α,*β*-unsaturated α-nitrosulfones were obtained similar to **10a**. Only in the case of *β*,*γ*-unsaturated α-nitrosulfone **7e** was no Michael adduct detectable. Since the phenyl group of **7e** would be in conjugation with the C,C double bond, **7e** would be strongly favored at the expense of the α,*β*-unsaturated α-nitrosulfone **8e**. Nevertheless, trapping evidence was obtained for the intermediacy of the α,*β*-unsaturated α-nitrosulfones even in the case of **7e** (vide infra).

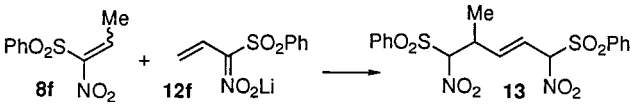


All of the bis(α-nitrosulfones), products of Michael addition, were obtained as mixtures of diastereomers: three diastereomers are possible and all were readily apparent for **10a**−**f**. All of the bis(α-nitrosulfones) were somewhat sensitive and difficult to purify by chromatography: indeed, **10c**, the most sensitive, could only be obtained in 80% purity. Structure assignment for **10b** is typical: diastereomer **i** (Figure 1) was assigned the structure of the racemate 1*R*,3*R*/1*S*,3*S* based on the observation of two equal intensity ^{1}H NMR doublets with chemical shifts of *δ* 6.67 and 6.08. The more downfield of these doublets exhibited a large coupling constant ($J_{1,2}$ = 5.7 Hz) and the more upfield a small coupling constant ($J_{2,3}$ = 1.9 Hz). The remaining two diastereomers **ii**−**iii** were assigned the structures of the meso diastereomers 1*R*,2*s*,3*S* and 1*R*,2*r*,3*S* based on the presence of only one ^{1}H NMR doublet each at *δ* 6.19 (major) and 6.14 (minor). The isomer ratio was 62:25:13 **i**, **ii**, and **iii**, respectively.

It is not possible, on the basis of the data accumulated, to provide an unambiguous assignment of the individual meso isomers. However, if it is assumed that these compounds adopt an extended conformation (Figure 1) where the large sulfone groups avoid each other, then the isomer with the larger coupling constant $J_{1,2}$ should correspond to the 1*R*,2*s*,3*S* isomer: thus, **ii** is probably the 1*R*,2*s*,3*S* isomer. In the case of 1,3-propanediol derivatives where a conformational preference exists owing to intramolecular H-bonding, similar, but more

definite, assignments have been made based upon coupling constants.[11]

Reaction of phenylsulfonylnitromethane with 2.3 molar equiv of LDA in tetrahydrofuran at −78 °C followed by sequential addition of acetaldehyde and glacial acetic acid led to the formation of the bis(α-nitrosulfone) **10f** in 80% yield. The bis(α-nitrosulfone) **10f** was obtained in approximately 95% purity as a 54:40:6 mixture of three diastereomers, **i**, **ii**, and **iii**, respectively. Also present in the crude products was a small amount of material tentatively identified as the β,γ-unsaturated bis(α-nitrosulfone) **13**, apparently formed via Michael addition of the nitronate **12f** to **8f** followed by deconjugation of the double bond. None of the simple β,γ-unsaturated α-nitrosulfone **7f** was detected in this reaction. It seems that here the α,β-unsaturated α-nitrosulfone was present at significantly higher equilibrium concentration than in the cases of **8a**−**e**. Perhaps the lack of a stabilizing alkyl group on the double bond of β,γ-unsaturated α-nitrosulfone **7f** might disfavor its formation. Typical monosubstituted alkenes (e.g., 1-butene) are approximately 2.5 kcal/mol less stable than trans-disubstituted alkenes.



In several cases, as little as 1.2 molar equiv of LDA led after acidification to formation of a mixture rich in **7** and **10** with varying amounts of remaining phenylsulfonylnitromethane. Thus, after formation of lithium salt **4**, its condensation with the aldehyde must have been occurring and required only a catalytic portion of strong base (i.e., the alternate condensation pathway not involving dianion **2** must have occurred). It is concluded that a low equilibrium concentration of the lithium alkoxide **5** must have been present and that deprotonation of **5** was occurring to afford the dilithium salt **3**. Perhaps further reaction was self-catalytic: dilithium salt **3**, likely the strongest base present during most of the reaction, could deprotonate more **5** affording **6** and another molecule of **3**. We were able to make use of this result since increased amounts (more than 50% of the crude product) of the bis(α-nitrosulfones) **10b**−**c** became available. Nevertheless, although the dianion **2** was not required for condensation, cleaner condensation to the β,γ-unsaturated α-nitrosulfone was observed when more than 2 molar equiv of LDA was employed, implicating the dianion **2** as the preferred intermediate.

Interconversion of the β,γ-unsaturated α-nitrosulfones **7** and the α,β-unsaturated α-nitrosulfones **8** was demonstrated under neutral buffered conditions. Thus, a pure sample of **7a** was allowed to react with phenylsulfonylnitromethane and lithium acetate/acetic acid in THF for 24 h affording conversion to a mixture of products containing bis(α-nitrosulfone) **10a**, **7a**, and phenylsulfonylnitromethane in a 13:42:45 mole ratio. The bis(α-nitrosulfone) **10a** must be forming via Michael addition to the α,β-unsaturated α-nitrosulfone **8a** and hence the presence of **8a** is required: it is surmised that an unfavorable equilibrium exists between the β,γ-unsaturated α-nitrosulfone **7a**, which is inert to Michael addition, and the α,β-unsaturated α-nitrosulfone **8a**, which undergoes Michael addition. Similarly, a pure sample of **7d** afforded a mixture of products containing bis(α-nitrosulfone) **10d**, **7d**, and phenylsulfonylnitromethane in a 27:34:40 mole ratio. Apparently, isomerization of **7d** is somewhat more facile than isomerization of **7a**.

(11) Barluenga, J.; Resa, J. G.; Olano. B.; Fustero, S. *J. Org. Chem.* **1987**, *52*, 1425.

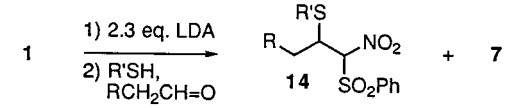
Table 2. Products Obtained from Thiol Trapping of α,β-Unsaturated α-Nitrosulfone Intermediates Derived from the Reaction of 2 with Aldehydes

$RCH_2CH{=}O$ R =	R′SH R′ =	β-sulfide yield,[a] %	*R*,S**/*R*,R** isomer ratio (crude) (pure[a])n	β,γ-unsaturated α-nitrosulfone yield, %
CH_3	Ph	**14a**, 83	(67:33) (100:0)	**7a**, 0
CH_3CH_2	$PhCH_2$	**14b**, 72[b]	(65:35) (65:35[b])	**7b**, 0
$PhCH_2$	CH_3CH_2	**14c**, 63	(75:25) (100:0)	**7c**, 18
Ph	Ph	**14d**, 61	(57:43) (100:0)	**7d**, 19

[a] After chromatography and subsequent crystallization. [b] Remained an oil.

It has not been established whether a single isomer or both possible isomers of the α,β-unsaturated α-nitrosulfone are present in the above reactions. However, molecular mechanics calculations suggest a 1.1 kcal/mol lower steric strain energy for the *Z*-isomer of **8f** compared to the *E*-isomer. A similar 1.0 kcal/mol lower steric strain energy was calculated for the *Z*-isomer of **8a** compared to the *E*-isomer. Also, by analogy to α,β-unsaturated α-nitrosulfides,[5] the *Z*-isomer of the α,β-unsaturated α-nitrosulfones would seem to be the preferred isomer.

The α,β-unsaturated α-nitrosulfone intermediate present in the tandem nitroaldol/dehydration reactions was purposefully intercepted to provide products of conjugate addition. Thus, various thiols were added to the dianion reaction mixture prior to the addition of aldehyde. In all four of the cases examined, the α,β-unsaturated α-nitrosulfone intermediate was intercepted by the thiol and little if any of the normal β,γ-unsaturated α-nitrosulfone was formed (Table 2). Thus, reaction of phenylsulfonylnitromethane with excess LDA in tetrahydrofuran at −78 °C followed by sequential addition of thiophenol, propanal and glacial acetic acid led to the formation of β-sulfide **14a** in 83% yield. The initial product was a mixture of diastereomers that was converted to a single diastereomer on crystallization, presumably the isomer with the stronger crystal lattice. The diastereomer with the larger coupling constant ($J_{1,2}$ = 11.2 Hz) observable for the α-proton was formed preferentially. Based on X-ray crystallographic data obtained for a single enantiomorphic crystal (pure 1*R*,2*R*-enantiomer) of the major isomer of **14a**, the *R*,R** configuration was assigned whereas the isomer with the smaller coupling constant ($J_{1,2}$ = 5.5 Hz) was assigned the *R*,S** configuration. The *R*,R** and *R*,S** diastereomers must interconvert in the liquid state, presumably via the nitronate intermediate, with the *R*,R** isomer crystallizing preferentially from solution to afford a conglomerate: perhaps the driving force for the isomerization is the preference of *R*,*R* and *S*,*S* isomers to crystallize separately.



In analogous fashion, the β-sulfides **14b**−**d** were prepared as initial diatereomeric mixtures from the appropriate thiols and aldehydes. In all cases the initial major isomer exhibited a large coupling constant ($J_{1,2}$ =

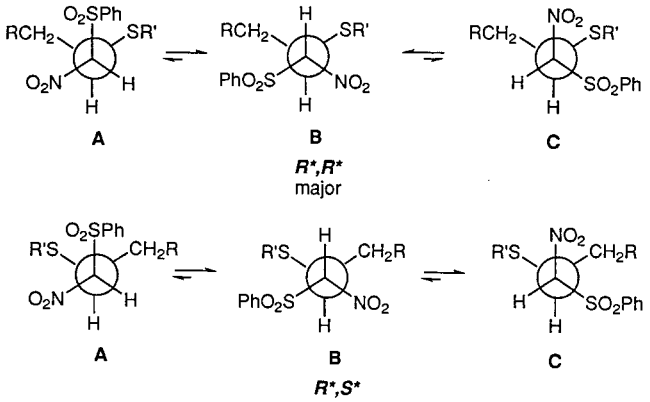


Figure 2. Conformations of the C_1-C_2 bond of β-sulfides **14a**−**d**.

9.2−11.2 Hz) for the α-proton while the minor isomer exhibited a small coupling constant ($J_{1,2}$ = 3.9−6 Hz). By analogy with **14a**, the isomer with the larger $J_{1,2}$ was assigned the *R**,*R** configuration. β-Sulfide **14b** did not crystallize and remained a 65:35 diastereomer mixture. However, β-sulfides **14c**,**d** crystallized affording conversion of the *R**,*S** isomer to the *R**,*R** isomer. In both cases, initial crystallization afforded a 95:5 *R**,*R**/*R**,*S** diastereomer ratio for the entire product which, with one recrystallization, afforded pure *R**,*R** diastereomer.

It is noteworthy that even the α,β-unsaturated α-nitrosulfone **8e** could be intercepted before isomerization to **7e** in which the double bond is in conjugation with the benzene ring. Here, β-sulfide **14d** was isolated as the major product. However, the β-sulfide **14d** was somewhat thermally sensitive. On warming **14d** to 50 °C, rapid elimination occurred and the β,γ-unsaturated α-nitrosulfone **7e** was formed.

Conformational isomers around the C_1-C_2 bond of the β-sulfides **14a**−**d** have been examined for the purpose of defining substituent interactions (Figure 2). For the *R**,*R**diastereomer, conformation **B** where protons are located anti must be major owing to the large coupling constants observed. Indeed, the crystallographic data obtained for **14a** clearly indicate conformation **B** as the preferred conformation in the crystalline state. Conformation **A** would be disfavored owing to steric hindrance to placing the bulky sulfone group simultaneously gauche to the thioether group and C_3 of the extended chain. Conformation **C** would be disfavored largely owing to an unfavorable steric interaction between the thioether and the sulfone groups.

For the *R**,*S**diastereomer, conformation **A** seems unlikely as a preferred conformation owing to steric hindrance from the thioether group and C_3 of the extended chain with the sulfone group. Conformation **C** must then be a favored conformation in order to explain the modest coupling constants observed. It is therefor concluded that placing the nitro group gauche to the thioether groups is favorable, strongly suggesting an attractive interaction. This also explains the preference for conformation **B** of the *R**,*R**diastereomer. Other workers have noted a preference for gauche conformations and apparent dipolar attractive interaction between the nitro and hydroxyl groups of nitro alcohols[12] and the nitro and alkoxyl groups of nitroethers.[13]

(12) Kingsbury, C. A.; Sopchik, A. E.; Underwood, G.; Rajan, S. *J. Chem. Soc., Perkin Trans. 2* **1982**, 867.

Conclusions

A simple procedure employing excess LDA for the formation of the dilithium salt of phenylsulfonylnitromethane has been developed. Condensation of this dilithium salt with unbranched aldehydes occurs readily but the resulting nitroaldols are sensitive and will rapidly dehydrate to β,γ-unsaturated α-nitrosulfones. An interesting tautomeric equilibration between β,γ-unsaturated α-nitrosulfones and the corresponding α,β-unsaturated α-nitrosulfones at or near pH 7 has been established. This equilibration, reminiscent of the equilibration between keto and enol tautomers, provides a low concentration of the reactive Michael-acceptor, the α,β-unsaturated α-nitrosulfone. The formation of bis(α-nitrosulfones) and β-sulfides via conjugate addition to the intermediate α,β-unsaturated α-nitrosulfones readily occurs, presaging their general use as novel Michael acceptors.

Experimental Section

General Methods. NMR spectra (250 MHz for ^1H in $CDCl_3$) were obtained as previously described[14] unless otherwise noted. High-resolution mass spectra were obtained using a VG ZAB-HS mass spectrometer.[15] Diisopropylamine (from CaH_2), acetaldehyde, propanal, butanal, and pentanal were freshly distilled just prior to use. Phenylsulfonylnitromethane was prepared by a published procedure.[1] All reactions were run under a nitrogen atmosphere.

Tandem Nitroaldol/Dehydration Reaction of 1 and Propanal. Butyllithium (1.9 mL of a 2.5 M solution in hexanes, 4.7 mmol) was added to a cold (dry ice) solution of diisopropylamine (0.49 g, 4.8 mmol) in THF (6 mL). The resulting solution was allowed to warm to −20 °C and was recooled (dry ice). A solution of phenylsulfonylnitromethane (**1**) (0.40 g, 2.0 mmol) in THF (4 mL) was added dropwise over a 10 min period to the first solution. The resulting yellow solution of dianion **2** was stirred for 1 h, allowed to warm to −40 °C, and recooled (dry ice). A solution of propanal (0.14 g, 2.4 mmol) in THF (10 mL) was added dropwise over 30 min and the resulting solution was stirred for an additional 30 min. Glacial acetic acid (5 mL) was added dropwise and the reaction solution was allowed to warm to room temperature. The reaction solution was poured into water that had been acidified with a few drops of concentrated hydrochloric acid. The resultant mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was kept at room temp for 12−24 h and was taken up in CH_2Cl_2 (50 mL). Alternatively, the crude product was warmed at 40−50 °C for 2 h during concentration and was taken up in CH_2Cl_2. Aqueous 5% NaOH (200 mL) was added, the resulting mixture was stirred for 10 min, and the CH_2Cl_2 layer containing propanal self-condensation products[16] was removed. The basic aqueous layer was washed with CH_2Cl_2 and acidified with concentrated aqueous HCl affording a milky-white mixture. This mixture was extracted with CH_2Cl_2, and the combined extracts were washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product at this stage typically consisted of **1** (2−5%), β,γ-unsaturated α-nitrosulfone **7a** (90−95%), and Michael adduct **10a** (2−5%). Further purification was either by procedure A or procedure B.

(13) Aebischer, B.; Hollenstein, R.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 1748.

(14) Wade, P. A.; Kondracki, P. A.; Carroll, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8807.

(15) We thank Dr. Jeffrey Honovich (Drexel University) for obtaining the mass spectra.

(16) ^1H NMR spectra of simple aldols from: Mahrwald, R.; Costisella, B.; Gundogan, B. *Synthesis* **1998**, 262. Aldol condensation side reactions under basic conditions are numerous; see: Nielsen, A. T.; Houlihan, W. J. In *Organic Reactions*; Nielsen, A. T., Houlihan, W. J., Assoc. Eds.; Wiley: New York; Vol. 16, p 1.

Procedure A was followed for crude product containing 2−3% **1**: Preparative TLC (CH_2Cl_2−HOAc, 98:2) removed the Michael adduct **10a** (less mobile fraction) but not **1**. In this way, nearly pure **7a** (0.43 g, 88% yield, 97% pure contaminated with 3% of **1**) was obtained as an oil from the more mobile band. Further purification by preparative TLC (CH_3CN-Et_2O, 50:50) gave material free of **1** in the upper half of the main band, providing the analytical sample: IR (film) 1562 (NO_2), 1335, 1156 (SO_2) cm^{-1}; ^1H NMR δ 7.6−7.9 (m, 5H), 6.15 (dq, 1H, J = 15.4, 6.7 Hz), 5.92 (d, 1H, J = 9.2 Hz), 5.70 (ddq, 1H, J = 15.4, 9.6, 1.7 Hz), 1.84 (dd, 3H, J = 6.7, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 142.3, 135.3, 134.0, 130.0, 129.2, 115.8, 103.1, 18.4; HRMS (M + Na^+, FAB, NaBr) calcd for $C_{10}H_{11}NO_4SNa$ 264.0306, found 264.0299.

The less mobile chromatography fraction afforded 12 mg (3% yield) of a relatively pure sample of **10a** consisting of three diastereomers **i**, **ii**, and **iii** in a 60:25:15 ratio, respectively) as an oil: ^1H NMR δ 7.6−8.1 (m, 10H), 6.65 (d, due to **i**, J = 6.3 Hz), 6.19 (d, due to **ii**, J = 6.5 Hz), 6.1 (d, 1H due to **i**, J = 2.0 Hz), 6.13 (d, 2H due to **iii**, J = 2.1 Hz), 3.8−3.95 (m, 1H), 2.3−2.55 (m) and 2.05−2.25 (m) (total 2H), 1.03 (m, 3H); HRMS (M + Na^+, FAB, NaBr) calcd for $C_{17}H_{18}N_2O_8S_2Na$ 465.0402, found 465.0393.

Procedure B was followed in cases where significant quantities (>3%) of **1** were present. First **1** was removed from the crude product by taking advantage of its more rapid rate of deprotonation compared to the other acidic products. Repetitive acid−base extractions afforded a slow acid fraction free of **1** and a fast acid fraction which was predominantly **1**. Thus, product contaminated with **1** was dissolved in CH_2Cl_2 (50 mL), and the solution was rapidly extracted with 5% sodium hydroxide (200 mL; mixing in a separatory funnel involved three quick inversions taking <20 s). The organic extracts were washed successively with 10% aqueous HCl and distilled water, dried over anhydrous Na_2SO_4, and concentrated to an oil. This oil contained β,γ-unsaturated α-nitrosulfone **7a** and Michael adduct **10a** but no **1**. The basic aqueous layer was acidified with concentrated HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated to afford a mixture enriched in **1** but containing some **7a**. This mixture was resubjected to the separation procedure: several (2−3) repetitions on the mixed fractions afforded more material free of **1** which was combined with the first fraction. The product free of **1** was then further purified by preparative TLC (CH_2Cl_2−HOAc, 98:2) to remove Michael adduct **10a** (less mobile fraction). However, a trace (1−2%) of **1** reformed during the final chromatographic purification. It was determined that unidentified impurities formed from a small amount of base-induced decomposition of **7a** were the source of the newly reformed **1**.[17] This procedure typically afforded 0.36−0.4 g (75−83% yield) of **7a** (98% pure, contaminated with 2% of **1**).

Tandem Nitroaldol/Dehydration Reaction of 1 and Acetaldehyde. The procedure employed for propanal was repeated using acetaldehyde (0.11 g, 2.4 mmol) in place of propanal. Purification (procedure B) as before gave only Michael adducts. The main product, obtained as an oil, was **7f** (0.69 g, 80% yield, 52:39:08 mixture of diastereomers **i**, **ii**, and **iii**, respectively): ^1H NMR δ 7.61−8.01 (m, 10H), 6.54 (d, 1H of **i**, J = 2.7 Hz), 6.36 (d, 1H of **i**, J = 10.0 Hz), 6.19 (d, 2H of **ii**, J = 6.6 Hz), 5.79 (d, 2H of **iii**, J = 6.0 Hz), 3.9−4.1 (m, 1H of **i**-**iii**), 1.97 (d, 3H of **iii**, J = 6.9 Hz), 1.68 (d, 3H of **i**, J = 6.8 Hz), 1.52 (d, 3H of **ii**, J = 6.7 Hz); ^{13}C NMR δ 137.05, 136.29, 135.99, 135.61, 134.75, 133.37, 129.84, 129.78, 129.63, 129.58, 101.61, 99.67, 97.0, 34.68, 32.65, 12.16, 11.83; HRMS (M + Na^+, FAB, NaBr) calcd for $C_{16}H_{16}N_2O_8S_2Na$ 451.0246, found 451.0244.

Obtained as an oil (55 mg, 6% yield) from a more mobile chromatography fraction was a compound which appears to be Michael adduct **13** (predominantly 3 of the 4 possible diastereomers: **i**, **ii**, and **iii** in a 2:1:1 ratio): ^1H NMR (500 MHz)[18] δ 7.53−7.96 (m, 5H); 6.30 (dd, J = 14.8, 8.4 Hz), 6.05−6.15 (m), 6.03 (d, J = 9.5 Hz), 5.98 (d, J = 9.6 Hz), 5.8−5.9 (m) 5.76 (dd, J = 9.2, 14.8 Hz), and 5.35−5.45 (m) (total 3H); 3.3−3.45 (m, major) and 3.2−3.3 (m, minor) total 1H, 1.42 (d, J = 6.8 Hz, isomer **i**), 1.20 (d, J = 6.8 Hz, isomer **ii**), and 1.14 (d, J = 6.7 Hz, isomer **iii**) (total 3H); HRMS (M + Na^+, FAB, NaBr) calcd for $C_{18}H_{18}N_2O_8S_2Na$ 477.0402, found 477.0410.

Tandem Nitroaldol/Dehydration Reaction of 1 and Butanal. The procedure employed for propanal was repeated using butanal (0.17 g, 2.4 mmol) in place of propanal. Purification (procedure B) as before gave 0.39 g (77% yield) of β,γ-unsaturated α-nitrosulfone **7b** from the most mobile chromatography fraction (CH_2Cl_2−HOAc, 98:2) as an oil: IR (film) 1562 (NO_2), 1336, 1156 (SO_2) cm^{-1}; ^1H NMR δ 7.6−7.9 (m, 5H), 6.2 (dt, 1H, J = 15.4, 6.2 Hz), 5.97 (d, 1H, J = 9.6 Hz), 5.65 (ddt, 1H, J = 15.4, 9.6, 1.6 Hz), 2.19 (m, 2H), 0.98 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 148.4, 135.3, 134.0, 130.0, 129.1, 113.8, 103.2, 25.7, 12.1; HRMS (M + Na^+, FAB, NaBr) calcd for $C_{11}H_{13}NO_4SNa$ 278.0463, found 278.0464.

Michael adduct **10b** (2% yield) was observed in the crude products (least mobile TLC fraction).

Tandem Nitroaldol/Dehydration Reaction of 1 and Pentanal. The procedure employed for propanal was repeated using pentanal (0.21 g, 2.4 mmol) in place of propanal. Purification (procedure B) as before gave 0.38 g (70% yield) of β,γ-unsaturated α-nitrosulfone **7c** from the most mobile chromatography fraction (CH_2Cl_2−HOAc, 98:2) as an oil: IR (film) 1560 (NO_2), 1344, 1157 (SO_2) cm^{-1}; ^1H NMR δ 7.6−7.9 (m, 5H), 6.13 (dt, 1H, J = 15.3, 6.8 Hz), 5.92 (d, 1H, J = 9.7 Hz), 5.64 (ddt, 1H, J = 15.3, 9.6, 1.5 Hz), 2.14 (m, 2H), 1.44 (app sx, 2H, J = 7.4 Hz), 0.92 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ 146.9, 135.1, 133.8, 129.8, 129.0, 114.6, 103.0, 34.3, 21.1, 13.3; HRMS (M + Na^+, FAB, NaBr) calcd for $C_{12}H_{15}NO_4SNa$ 292.0619, found 292.0618.

Michael adduct **10c** (1% yield) was observed in the crude products (least mobile TLC fraction).

Preparation of Michael Adduct 10b. To obtain a workable quantity of the Michael adduct **10b**, a modified tandem nitroaldol dehydration procedure was followed. Less base (2.4 mmol of LDA) was employed keeping the amount of phenylsulfonylnitromethane (**1**) (0.40 g, 2.0 mmol) and butanal (0.17 g, 2.4 mmol) as before. Further reaction and workup as before gave variable amounts of **7b**, **1**, and Michael adduct **10b**: however, much more Michael adduct was noted than when 4 mmol of base was employed. Indeed, the crude products routinely consisted of more **10b** than **7b**. Purification (procedure B) as before followed by preparative TLC afforded a purified sample of **10b** (0.20 g, 22% yield: >95% pure by ^1H NMR; least mobile fraction) consisting of three diastereomers **i**, **ii**, and **iii** in a 62:25:13 ratio, respectively: IR (film) 1565 (NO_2), 1341, 1153 (SO_2) cm $^{-1}$; ^1H NMR δ 7.5−8.1 (m, 5H), 6.67 (d, 1H of **i**, J = 5.7 Hz), 6.19 (d, 2H of **ii**, J = 6.4 Hz), 6.14 (d, 2H of **iii**, J = 1.8 Hz), 6.08 (d, 1H of **i**, J = 1.9 Hz), 3.95−4.05 (m, 1H), 2.3−2.5 (m) and 1.95−2.1 (m) (total 2H), 1.2−1.55 (m, 2H), 0.8−1.0 (m, 3H); HRMS (M + Na^+, FAB, NaBr) calcd for $C_{18}H_{20}N_2O_8S_2Na$ 479.0559, found 479.0578.

Preparation of Michael Adduct 10c. The procedure for preparing **10b** was followed substituting pentanal (0.21 g, 2.4 mmol) for butanal. Further reaction and workup as before gave a mixture of **7c**, **1**, and **10c**. Here the crude product ratios were quite variable from run to run. In some cases β,γ-unsaturated α-nitrosulfone **7c** was the major product but in other cases the crude product consisted of more Michael adduct than **7c**. Purification (procedure B) of crude product rich in **10c** followed by preparative TLC afforded 94 mg of a partially purified sample of **10c** (least mobile fraction; 10% isolated yield, 80% pure contaminated predominantly by **1**) consisting of three diastereomers **i**, **ii**, and **iii** in a 67:23:10 ratio, respectively: IR (film) 1565 (NO_2), 1341, 1154 (SO_2) cm $^{-1}$; ^1H NMR δ 7.5−8.1 (m, 5H), 6.67 (d, 1H of **i**, J = 5.6 Hz), 6.19 (d, 2H of **ii**, J =

(17) This matter is under investigation. The fate of the 3-carbon side-chain is not known when **1** is regenerated. However, it is known that repetitive chromatography does not increase the amount of **1** (i.e., β,γ-unsaturated α-nitrosulfone **7a** is not reverting to **1** on silica gel).

(18) We thank Dr. Hu Liu (University of Pennsylvania) for obtaining the spectra.

6.2 Hz), 6.14 (d, 2H of **iii**, $J = 1.9$ Hz), 6.07 (d, 1H of **i**, $J = 1.9$ Hz), 3.9−4.0 (m, 1H), 2.0−2.5 (m, 2H), 1.2−1.55 (m, 4H), 0.8−1.0 (m, 3H); HRMS (M + Na^+, FAB, NaBr) calcd for $C_{19}H_{22}N_2O_8S_2Na$ 493.0715, found 493.0705.

Three attempts to further purify **10c** by additional preparative TLC led to less pure samples in each case. The **1** present could be removed but an increased amount of unidentified materials was obtained.

Tandem Nitroaldol/Dehydration Reaction of 1 and 3-Phenylpropanal. The procedure employed for propanal was repeated using 3-phenylpropanal (0.32 g, 2.4 mmol) in place of propanal. Purification (procedure B) as before gave β,γ-unsaturated α-nitrosulfone **7d** (0.33 g, 52% yield) as an oil: IR (film) 1562 (NO_2), 1337, 1156 (SO_2) cm^{-1}; ^1H NMR δ 7.06−8.0 (m, 10H), 6.28 (dt, 1H, $J = 15.3$, 6.7 Hz), 5.92 (d, 1H, $J = 9.6$ Hz), 5.68 (ddt, 1H, $J = 15.3$, 9.6, 1.5 Hz), 3.4−3.6 (m, 2H); ^{13}C NMR δ 145.1, 137.1, 135.2, 133.8, 130.0, 129.2, 128.6, 128.5, 126.7, 115.9, 103.0, 38.8; HRMS (M + Na^+, FAB, NaBr) calcd for $C_{16}H_{15}NO_4SNa$ 340.0619, found 340.0610.

Preparative TLC (least mobile fraction) afforded 0.10 g (10% yield) of a purified sample of **10d** consisting of three diastereomers **i**, **ii**, and **iii** in a 65:25:10 ratio, respectively: IR (film) 1559 (NO_2), 1341, 1154 (SO_2) cm^{-1}; ^1H NMR δ 7.55−8.0 (m, 5H), 7.1−7.4 (m, 5H), 6.67 (d, 1H of **i**, $J = 5.7$ Hz), 6.21 (d, 2H of **ii**, $J = 6.4$ Hz), 6.10 (d, 2H of **iii**, $J = 2.2$ Hz), 6.03 (d, 1H of **i**, $J = 2.2$ Hz), 4.0−4.08 (m, 1H), 2.3−3.0 (m, 4H); HRMS (M + Na^+, FAB, NaBr) calcd for $C_{23}H_{22}N_2O_8S_2Na$ 541.0712, found 541.0715.

Tandem Nitroaldol/Dehydration Reaction of 1 and Phenylacetaldehyde. The procedure employed for propanal was repeated using phenylacetaldehyde (0.29 g, 2.4 mmol) in place of propanal. Purification (procedure B) as before gave β,γ-unsaturated α-nitrosulfone **7e** (0.45 g, 75% yield) as an oil that crystallized from benzene/hexanes (33:67): mp 120.5−121.5 °C; IR (film) 1560, 1340, 1152 cm^{-1}; ^1H NMR δ 7.55−7.95 (m, 5H), 7.35−7.45 (m, 5H), 6.92 (d, 1H, $J = 15.5$ Hz), 6.23 (dd, 1H, $J = 15.5$, 9.6 Hz), 6.10 (d, 1H, $J = 9.7$ Hz); ^{13}C NMR δ 142.9, 135.4, 134.0, 133.8, 130.1, 129.9, 129.1, 128.8, 127.3, 112.3, 103.6. Anal. Calcd for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62. Found: C, 59.43; H, 4.32; N, 4.51.

None of the Michael adduct **10e** could be detected in the crude reaction products.

Reaction of Phenylsulfonylnitromethane with β,γ-Unsaturated α-Nitrosulfone 7a. A solution containing phenylsulfonylnitromethane (63 mg, 0.31 mmol), alkene **7a** (73 mg, 0.30 mmol), $LiOAc{\cdot}H_2O$ (150 mg, 1.47 mmol), and glacial HOAc (0.78 g, 13 mmol) in THF (7 mL) was stirred at rt for 24 h. Volatiles were removed in vacuo, and the residue was partitioned between water and CH_2Cl_2. The layers were separated, and the CH_2Cl_2 layer was washed with water, dried, and concentrated at reduced pressure to afford an oil (124 mg, 91% recovery of material). This oil by ^1H NMR consisted of **7a**, **1**, and **10a** in a 42:45:13 mole ratio, respectively. Longer reaction times resulted in an increased percentage of **10a** but a much reduced material balance.

Reaction of Phenylsulfonylnitromethane with β,γ-Unsaturated α-Nitrosulfone 7d. The procedure employed for **7a** was repeated using alkene **7d** (95 mg, 0.30 mmol) instead. An oil (138 mg, 87% recovery of material) was obtained. This oil by ^1H NMR consisted of **7d**, **1**, and **10d** in a 34:40:27 mole ratio, respectively.

Reaction of 1 and Propanal. Observation of Nitroaldol 9a. The first procedure employed for propanal was repeated except more butyllithium (7.0 mmol), diisopropylamine (0.74 g, 7.3 mmol), and propanal (0.42 g, 7.2 mmol) were employed and the products were examined *immediately* after removal of CH_2Cl_2, prior to sitting and without warming. Two diastereomers of nitroaldol **9a** (60:40 ratio, **i**/**ii**) were apparent by ^1H NMR: δ 5.56 (d, 1H of **ii**, $J = 8.6$ Hz) overlapping 5.54 (d, 1H of **i**, $J = 6.2$ Hz), 4.42 (ddd, 1H of **i**, $J = 8.6$, 6.2, 4.0), 4.34 (1H of **ii**, app td), 1.5−1.8 (m, 2H), 0.9−1.1 (m, 3H). These bands decreased with time. Other bands attributable to **7a**, **1**, **10a**, and propanal self-condensation were also observed. The IR showed a broad band at 3100−3600 cm^{-1} (OH) which gradually decreased with time. In the mass spectrum (CI, CH_4), an ion *m*/*z* 260 (*m* + 1 for **9a**) was observed which decreased on aging of the sample compared to an ion *m*/*z* 242 (*m* + 1 for **7a**).

Reversion of Nitroaldol 9a to 1. A solution of crude nitroaldol (155 mg; **9a**, **7a**, and **1** 57:32:10, respectively) in CH_2Cl_2 was rapidly extracted with 5% aqueous NaOH. Acidification (con HCl to pH 1−3) of the aqueous layer and extraction with CH_2Cl_2 afforded, after workup, a mixture (125 mg; **1** and **7a**, 59:41) free of nitoaldol **9a** and enriched in phenylsulfonylnitromethane. The original CH_2Cl_2 layer was washed with 10% aqueous HCl and water and was dried. Concentration afforded 23 mg of alkene contaminated with several unidentified products, in part those derived from simple aldol condensation of propanal.

Reaction of 1 and Propanal. Observation of β-Amine 11. The first procedure employed for propanal was repeated except the products were examined *immediately* after removal of CH_2Cl_2, prior to sitting and without warming. Crude products consisted of **11** (25%), **7a** (70%), and Michael adduct **10a** (5%) as well as small amounts of propanal self-condensation products and acetic acid. Acetic acid was removed by entrainment with CCl_4 (three 10-mL portions, sequentially evaporated in vacuo at 20 °C). Two diastereomers **i** and **ii** of **11** (65:35 ratio, respectively) were apparent by ^1H NMR: δ 6.69 (d, 1H of **ii**, $J = 10.4$ Hz), 6.56 (d, 1H of **i**, $J = 10.5$ Hz), 4.1−4.25 (m, 1H of **ii**), 3.97 (app dt, 1H of **i**, $J = 3.8$, 10.4 Hz), 3.2−3.4 (broad s, 2H of **i,ii**), 2.1−2.5 (m, 2H of **i,ii**), 1.20 (d, 6H of **i,ii**, $J = 6.5$ Hz), 0.9−1.05 (m, 3H of **i,ii**). Other overlapping bands and bands attributable solely to **7a**, **10a**, and propanal self-condensation were also apparent.

Stoichiometry of LDA Reaction with Phenylsulfonylnitromethane (1). Two 3.0-mL aliquots of LDA solution (approximately 0.8 M) were prepared as described under "Tandem nitroaldol/dehydration reaction of **1** and propanal" and were kept cold (dry ice). Triphenylmethane (2 mg) was added to each, and an intense red color rapidly developed. The first aliquot was titrated with a solution of benzoic acid (0.305 g) in THF (2 mL) to disappearance of the red color. The remaining portion of solution containing benzoic acid was concentrated and the unused amount of benzoic acid was weighed and subtracted from the total amount. In this way, it was determined that 0.269 g (2.20 mmol) of benzoic acid had been consumed and that the titrated solution was 0.73 M in LDA. The second aliquot was titrated with a solution of **1** (0.503 g) in THF (2 mL) to disappearance of red color (light yellow end point). The unused portion of solution containing **1** was concentrated and the amount of the recovered **1** was subtracted from the total to determine the amount consumed: 0.190 g (0.95 mmol). A duplicate run gave similar results.

Tandem Nitroaldol/Dehydration Reaction of 1 and Propanal in the Presence of Thiophenol: Isolation of β-Sulfide 14a. A cold (dry ice) THF solution of dianion **2** was prepared from butyllithium (7.0 mL of a 2.0 M solution in cyclohexane, 14 mmol), diisopropylamine (1.67 g, 16.5 mmol), phenylsulfonylnitromethane (**1**) (0.50 g, 2.5 mmol), and THF (15 mL) as described previously. Thiophenol (0.42 g, 3.8 mmol) was added dropwise over 1 min followed by a solution of propanal (0.22 g, 3.7 mmol) in THF (15 mL) added dropwise over 30 min. The resulting solution was stirred for an additional 30 min. Glacial acetic acid (20 mL) was added dropwise, and the reaction solution was allowed to warm to room temperature. Workup as previously described afforded the crude product which was kept at room temp for 12−18 h. Examination of the crude product by ^1H NMR indicated β-sulfide **14a** (67:33, diastereomer ratio) and diphenyl disulfide as the major products present. Diphenyl disulfide was removed by rapid chromatography on silica gel (CH_2Cl_2−hexanes, 50:50 elution) without noticeable change in the diastereomer ratio for **14a** (0.73 g, 83% yield) obtained as an oil. However, the entire portion of purified oil crystallized to afford the *R*,R** isomer exclusively. The analytical sample of **14a** was recrystallized from benzene/hexanes: mp 96−97 °C; IR (KBr) 1551 (NO_2), 1338, 1316, 1158 (SO_2) cm^{-1}; ^1H NMR δ 7.3−7.9 (m, 10H), 5.50 (d, 1H, $J = 11.2$ Hz), 3.60 (app td, 1H, $J = 2.9$, 10.9 Hz), 2.25−2.40 (m, 1H), 1.5−1.7 (m, 1H), 1.25 (t, 3H, $J =$

7.2 Hz); ^{13}C NMR δ 135.6, 135.2, 134.3, 129.9, 129.5, 129.4, 129.3, 105.1, 50.4, 22.7, 11.1; HRMS (M + Na^+, FAB, NaBr) calcd for $C_{16}H_{17}NO_4S_2Na$: 374.0497, found 374.0501. Anal. Calcd for $C_{16}H_{17}NO_4S_2$: C, 54.68; H, 4.87; N, 3.98. Found: C, 54.76; H, 4.74; N, 3.95.

Independent spectral bands present for the mixture of diastereomers attributed to the *R*,S** isomer of **14a**: ^{1}H NMR δ 5.48 (d, 1H, J = 5.5 Hz), 3.6−3.7 (m, 1H), 2.1−2.25 (m, 1H), 1.22 (t, 3H J = 7.2 Hz); ^{13}C NMR δ 135.5, 135.4, 133.8, 129.8, 129.7, 102.5, 49.6, 22.7, 12.0.

Tandem Nitroaldol/Dehydration Reaction of 1 and Butanal in the Presence of α-Toluenethiol: Isolation of β-Sulfide 14b. The procedure employed for the preparation of **14a** was repeated with α-toluenethiol (0.47 g, 3.8 mmol) in place of thiophenol and butanal (0.53 g, 7.4 mmol) in place of propanal. After chromatography, β-sulfide **14b** (0.68 g, 72% yield) was obtained as a noncrystallizable oil consisting of a 65:35 mixture of *R*,R** and *R*,S** diastereomers, respectively: IR (film) 1562 (NO_2), 1338, 1153 (SO_2) cm $^{-1}$; ^{1}H NMR δ 7.5−7.9 (m, 5H), 7.05−7.3 (m, 5H), 5.46 (d, 1H *R*,R**, J = 10.7 Hz), 5.24 (d, 1H *R*,S**, J = 5.6 Hz), 3.72 (s, 2H, *R*,S**) 3.57 (d, 1H *R*,R**, J = 13.0 Hz), 3.53 (d, 1H *R*,R**, J = 13.0 Hz), 3.31 (ddd, 1H *R*,S**, J = 2.5, 5.6, 10.4 Hz), 3.19 (app td, 1H *R*,R**, J = 2.9, 10.3 Hz), 1.9−2.05 (m, 1H *R*,R**), 1.75−1.9 (m, 1H *R*,S**), 1.3−1.6 (m, 2H), 1.0−1.3 (m, 1H), 0.74 (t, *R*,S**, J = 7.3 Hz) overlapping 0.70 (t, *R*,R**, J = 7.4 Hz) [3H total]; ^{13}C NMR δ 137.0, 136.7, 136.0, 135.5, 135.2, 134.6, 129.9, 129.5, 129.4, 129.3, 129.2, 129.1, 128.9, 128.6, 127.6, 127.5, 105.7, 103.9, 43.6, 43.5, 37.1, 36.7, 33.0, 32.1, 20.0, 18.9, 13.4, 13.3; HRMS (M + Na^+, FAB, NaBr) calcd for $C_{18}H_{21}NO_4S_2Na$ 402.0809, found 402.0809.

Tandem Nitroaldol/Dehydration Reaction of 1 and 3-Phenylpropanal in the Presence of Ethanethiol: Isolation of β-Sulfide 14c. The procedure employed for the preparation of **14a** was repeated with ethanethiol (0.23 g, 3.8 mmol) in place of thiophenol and 3-phenylpropanal (0.51 g, 3.8 mmol) in place of propanal. After addition of the aldehyde, more of the volatile ethanethiol (0.23 g, 3.8 mmol) and again after addition of acetic acid still more ethanethiol (0.92 g, 14.9 mmol) was added. Volatiles were not stripped until after 12 h. Chromatography of the crude products afforded **14c** (g 75:25 *R*,R*/R*,S** ratio, 0.60 g, 63% yield) as the more mobile fraction. This purified material crystallized affording predominantly the *R*,R** isomer (95:5 *R*,R*/R*,S** ratio) of **14c** as a solid. The analytical sample of pure (*R*,R**)-**14c** was recrystallized from benzene/hexanes: mp 105−106.5 °C; IR (KBr) 1551 (NO_2), 1333, 1311, 1153 (SO_2) cm $^{-1}$; ^{1}H NMR δ 7.5−7.9 (m, 5H), 7.2−7.4 (m, 5H), 5.59 (d, 1H, J = 10.9 Hz), 3.39 (app td, 1H, J = 3.2, 10.4 Hz), 3.0−3.15 (m, 1H), 2.75−2.9 (m, 1H), 2.55 (q, J = 7.4 Hz) overlapping 2.55−2.7 (m)[3H total], 2.0−2.15 (m, 1H), 1.21 (t, 3H, J = 7.4 Hz); ^{13}C NMR δ 140.3, 135.6, 134.5, 129.9, 129.5, 128.6, 126.3, 105.6, 44.6, 32.7, 32.1, 26.5, 14.4; HRMS (M + Na^+, FAB, NaBr) calcd for $C_{18}H_{21}NO_4S_2Na$ 402.0810, found 402.0814. Anal. Calcd for $C_{18}H_{21}NO_4S_2$: C, 56.97; H, 5.58; N, 3.69. Found: C, 57.37; H, 5.49; N, 3.91.

Independent spectral bands present for the mixture of diastereomers attributed to the *R*,S** isomer of **14c**: ^{1}H NMR δ 5.63 (d [one band coincident with *R*,R** isomer], 1H, J = 6 Hz), 2.3−2.5 (m, 1H), 1.8−2.0 (m, 1H), 1.19 (t, 3H, J = 7.3 Hz).

Chromatography also afforded the β,γ-unsaturated α-nitrosulfone **7d** (0.14 g, 18% yield) as a less mobile fraction.

Tandem Nitroaldol/Dehydration Reaction of 1 and Phenylacetaldehyde in the Presence of Thiophenol: Isolation of β-Sulfide 14d. The procedure employed for the preparation of **14a** was repeated with phenylacetaldehyde (0.44 g, 3.7 mmol) in place of propanal. Examination of the crude product by ^{1}H NMR indicated β-sulfide **14d** (57:43, diastereomer ratio) and β,γ-unsaturated α-nitrosulfone **7e** as the major products present. Thin-layer chromatography afforded **7e** (0.14 g, 19% yield) as the less mobile fraction and crystalline **14d** (0.68 g, 61% yield, 95:5 *R*,R*/R*,S** ratio) as the more mobile fraction. The analytical sample of **14d** was recrystallized from benzene-hexanes: mp 112−113 °C; IR (KBr) 1551 (NO_2), 1333, 1311, 1153 (SO_2) cm $^{-1}$; ^{1}H NMR δ 7.1−8.0 (m, 10H), 5.67 (d, 1H, J = 9.9 Hz), 4.00 (app td, 1H, J = 3.6, 10.4l), 3.72 (dd, 1H, J = 14.5, 3.6 Hz), 2.83 (dd, 1H, J = 14.5, 10.7 Hz); ^{13}C NMR δ 135.7, 134.8, 134.5, 131.2, 130.0, 129.6, 129.5, 129.1, 129.0, 128.6, 127.2, 104.8, 50.5, 36.6; HRMS (M + Na^+, FAB, NaBr) calcd for $C_{21}H_{19}NO_4S_2Na$ 436.0653, found 436.0645. Anal. Calcd for $C_{21}H_{19}NO_4S_2$: C, 60.99; H, 4.63; N, 3.38. Found: C, 60.90; H, 4.55; N, 3.15.

Independent spectral bands present for the mixture of diastereomers attributed to the *R*,S** isomer of **14d**: ^{1}H NMR δ ^{1}H NMR δ 5.55 (d, 1H, J = 3.9 Hz), 4.0−4.1 (m, 1H), 3.87 (dd, 1H, J = 14.8, 2.3 Hz), 2.89 (dd, 1H, J = 11.1, 14.8 Hz).

Supporting Information Available: ^{1}H NMR spectra of **7a**−**d**, **10a**−**d**,**f**, **11**, **13**, and **14a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0000170