A STUDY OF ENDOCYCLIC NUCLEOPHILIC SUBSTITUTION AT SULFUR(VI) (SULFONATE ESTERS)

DEBRA J. MACINTYRE-ZOLLER

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A STUDY OF ENDOCYCLIC NUCLEOPHILIC SUBSTITUTION AT SULFUR(VI)

BY

DEBRA J. MACINTYRE-ZOLLER
BS in Chemistry, West Chester University, 1980

A DISSERTATION

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DEDICATION

This dissertation is dedicated to the Lord God.

"Give thanks to the Lord, for he is good.
His love endures forever."

Psalm 136:1, NIV
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ABSTRACT

A STUDY OF ENDOCYCLIC NUCLEOPHILIC
SUBSTITUTION AT SULFUR(VI)

by

Debra J. MacIntyre-Zoller
University of New Hampshire, December, 1985

To investigate the effect of geometry on nucleophilic substitution at sulfur(VI), a search was made for examples of endocyclic substitution. Substrate molecules were synthesized and then treated with strong bases, n-butyllithium or lithium diisopropylamide, in order to deprotonate a nitrogen or carbon so as to create a nucleophile which could attack a sulfonyl sulfur atom intramolecularly with displacement of a leaving group from the latter. The desired substitution was observed in several molecules. Deuterium-labeled substrates were prepared and crossover experiments were run to determine whether or not these reactions were intramolecular. One case involving a four-membered cyclic intermediate or transition state, the reaction of N-methyl-N-phenyl-4-toluenesulfonamide with n-butyllithium, proved to be intramolecular. Another case involving a five-membered
cyclic intermediate or transition state, the reaction of 2-aminoaryl arenesulfonates with strong bases, proved to be intramolecular. A third case which had the potential to involve a six-membered cyclic intermediate or transition state, the reaction of 2′-(N-methylaminomethyl)phenyl-4-toluenesulfonate, proved to be intermolecular. No stereochemical investigations were undertaken.
There are generally three types of sulfur in organic sulfur compounds: dicoordinate divalent sulfur, tricoordinate tetravalent sulfur, and tetracoordinate hexavalent sulfur. Nucleophilic substitution reactions at sulfur have been reviewed for these three types of sulfur.1-6 Further information on endocyclic nucleophilic substitution at sulfur is found in the Ph.D. dissertations of Yildiz and Chumpradit.7,8 This dissertation deals primarily with endocyclic substitution at tetracoordinate sulfur(VI).

The first example in which the stereochemistry of nucleophilic substitution at tetracoordinate sulfur(VI) was established was described by Sabol and Andersen.9 When (-)-menthyl (S)-phenylmethanesulfonate-16O, 18O, (1), was treated with 4-tolylmagnesium bromide, optically active benzyl p-tolyl sulfone-16O, 18O (2) was obtained (Scheme 1).
Scheme 1: Stereochemical Study of Nucleophilic Substitution at Sulfur(VI).

The configurations of sulfonate ester 1 and sulfone 2 were assigned in the following manner. (-)-Menthyl (R)-phenylmethanesulfinate (3) was oxidized to (-)-menthyl (S)-phenylmethanesulfonate (1) using potassium permanganate (90.2% $^{18}$O) in acetone. The assumption was made that this oxidation proceeded with retention, as it does in the oxidation of sulfilimines, so sulfonate ester 1 was assigned configuration $S$ at sulfur. Stirling$^{10}$ oxidized (R)-benzyl p-tolyl sulfoxide (4) to sulfone 2 utilizing $^{18}$O-labeled peracetic acid. Both the sulfone obtained by Sabol and
Andersen in the Grignard reaction (1 to 2) and the one obtained by Stirling (4 to 2) were levorotatory in chloroform and thus of the same configuration. It was assumed that the peracetic acid oxidation proceeded with retention; thus sulfone 2 must have configuration 3 at sulfur. It was concluded, therefore, that nucleophilic attack of 4-tolylmagnesium bromide on sulfonate ester 1 proceeded with inversion of configuration at sulfur.

This reaction could be concerted and involve an $S_N^2$-like transition state. Alternatively, it could involve an addition-elimination mechanism where the nucleophile adds to the sulfur, forming a trigonal bipyramidal intermediate (eq. 1) followed by elimination of the leaving group to form the product. The question of whether a stepwise mechanism or a concerted mechanism is operative, is still disputed.

$$\begin{align*}
R\text{SOR}' & \cdot \text{Nu}^- \rightarrow R\text{SOR}'\text{O}^\ominus \\
& \rightarrow R\text{SO}\text{Nu}^\ominus
\end{align*}$$

Engberts et al.\textsuperscript{11} presented evidence for the formation of a pentacoordinate sulfur intermediate in the intramolecular carboxyl-catalyzed hydrolysis of sulfonamides (Scheme 2).
Scheme 2: Intramolecular Carboxyl-catalyzed Hydrolysis of Sulfonamides.

By using Jaffe's extended Hammett equation (log $k_X/k_H = \rho_1 \sigma_1 + \rho_2 \sigma_2$), a value of (-0.54 ± 0.02) was obtained which is small but unmistakably negative. This value is consistent with a reduction in electron density on the carboxyl group in the transition state compared with the initial state. This was explained by postulating that the new oxygen-sulfur bond was fully formed in the transition state. The leaving group (NHR$_2$) value is very small and negative, signifying that the leaving group must carry a small partial positive charge in the transition state. The value for the sulfonyl center ($SO_2^-$) is -0.53, indicating a reduction
in electron density on going to the transition state. The simplest transition state to fit the requirement that all three centers—carboxyl, sulfonamide sulfur, and the leaving group nitrogen—are more electron deficient than in the initial state, is one which involves the breakdown of a pentacoordinate intermediate. Engberts therefore proposed a stepwise mechanism involving the pentacoordinate intermediate (Scheme 2).

Using ab initio studies on a simplified model of the above pentacoordinate intermediate, structure 5 was predicted to be the most favored of the possible structural alternatives where placement of the ligands was varied. The ring of the actual compound would be attached via apical and equatorial positions and the CSO angle would be about 90°. The nucleophile and leaving group were placed in diapical positions.

Engberts discussed kinetic salt effects and the
Thorpe-Ingold effect\textsuperscript{14} in the intramolecular carboxyl-catalyzed hydrolysis of alkyl sulfonamides. All of the previously mentioned examples of Engbert's work on this reaction have been exocyclic systems, where the leaving group, (NHR\textsubscript{2}), is expelled from the parent molecule.

Williams et al.\textsuperscript{15} presented evidence for a single transition state and, therefore, a concerted mechanism in the sulfonyl group (ArSO\textsubscript{2}^-) transfer between 4'-nitrophenyl 4-nitrobenzenesulfonate and various oxyanions (Scheme 3). The oxyanions that were used were not sterically hindered species nor α nucleophiles.

![Scheme 3: Sulfonyl Group Transfer Between Substituted Phenoxides.](image)

These reactions were demonstrated to involve nucleophilic attack by the oxyanions, rather than general base catalyzed hydrolysis by (1) the isolation of a
theoretical yield of the phenyl ester when the 4-nitrophenyl ester was reacted with phenolate buffers, (2) the observation of a negligible deuterium isotope effect \( \frac{k_{A\text{CO}}}{k_{A\text{C}}^D} = 0.93 \), and (3) the reaction of hindered reagents (2,2-diethylmalonate dianion and 2,4,6-collidine) with the 4-nitrophenyl ester which gave reactivities an order of magnitude below that calculated from the Brönsted-type equation given below.

If a stepwise mechanism were operative, a change in the rate-determining step would have occurred as the acceptor became more or less basic than the leaving group, 4-nitrophenoxide, signifying two electronically different transition states. When there is no difference in donor and acceptor basicities (\( \Delta pK=0 \)), then the displacement involves a symmetrical transition state. For a stepwise mechanism, a nonlinear Brönsted relationship should be observed, with a break at \( \Delta pK=0 \). For a concerted mechanism, a linear or gently curving Brönsted correlation should be observed.

The second-order rate constants of the reaction of oxyanions with 4-nitrophenyl 4'-nitrobenzenesulfonate obey the linear plot: \( \log k_{XO^-/q} = (0.54 \pm 0.11) (pK_{XOH} + \log p/q) - (7.8 \pm 0.3) \), \((r=0.986)\). These results indicate there is no substantial change in transition state structure over a range of eight \( pK \) units of the oxyanions; therefore, the transition state is symmetrical. This evidence for a single transition state was also supported by the reaction
of phenoxide ion with a series of aryl esters of
4-nitrobenzenesulfonic acid, which obeys a linear
Brönsted-type relationship: \( \log k_{\text{PhO}} = (-0.91 \pm 0.09) \)
\( \text{pK}_{\text{LG}} + (5.80 \pm 0.60) \), \( (r=0.991) \).

\[
\begin{align*}
\text{NHCOR} & \quad \text{OH}^\ominus \\
\text{SO}_2\text{OAr} & \quad \text{CR} \\
\text{6} & \quad \text{SO}_2 \\
\text{NHCOR} & \quad \text{OH}^\ominus \\
\text{H}_2\text{O} & \quad \text{SO}_2 \\
\text{7} & \quad \text{9} \\
\end{align*}
\]

Williams and Thea \(^{16}\) report that the hydrolysis of
sulfonate ester 6 by intramolecular amide group
assistance goes through the intermediate 7, (eq. 2).
They observed a large negative \( \rho \) value for the leaving group
variation, indicating that there is a considerable charge
increase on the leaving oxygen (OAr) on going from the
ground state to the transition state. This is consistent
with extensive S-O bond fission in the transition state 9.

Williams \textit{et al.} \(^{17}\) presented evidence to
support a concerted mechanism in the sulfate group
(-SO\(_3\)) transfer between isoquinoline-\(N\)-sulfonate
and substituted pyridines, (eq. 3). A Brønsted-type study was conducted between pH 7 and 8. The reaction obeyed good pseudofirst-order kinetics and followed the rate law:

$$k_{\text{obs}} = k_{\text{buffer}} + k_{H,0} + k_{X_{\text{pyr}}} [X_{\text{pyr}}].$$

General base catalysis was excluded by the observation that the rate of 2,6-lutidine was two orders of magnitude lower than that predicted by the Brønsted equation.

If a stepwise mechanism were operative, a Brønsted plot of log $k_{X_{\text{pyr}}}$ versus $pK_{X_{\text{pyr}}}$ would have exhibited a break at the $pK$ corresponding to isoquinoline. If a concerted mechanism were operative, a linear plot was expected. The reaction obeyed the linear plot: log $k_{X_{\text{pyr}}} = (0.23 \pm 0.002) pK_{X_{\text{pyr}}} - (1.92 \pm 0.04)$, ($r=0.995$). The observation of a linear relationship excluded the stepwise mechanism but was consistent with the
concerted mechanism.

A study done by Williams and coworkers on sulfate group transfer between substituted pyridines and phenols in aqueous solution also supported a single transition state; i.e., a concerted mechanism, (Scheme 4, path a).

\[
\begin{align*}
\text{Y} & \quad \text{ArO}^- \\
\text{N} & \quad \text{S} \\
\text{O} & \quad \text{OAr}
\end{align*}
\]

\[
\begin{align*}
\text{Y} & \quad \text{ArOSO}_3^- \\
\text{N} & \quad \text{S} \\
\text{O} & \quad \text{OAr}
\end{align*}
\]

Scheme 4: Sulfate Group Transfer Between Substituted Pyridines and Phenols.

The equilibrium constant for the reaction was given by the expression: \(\log K_{eq} = (1.74 \pm 0.1) \ pK_{ArOH} - (1.24 \pm 0.02) \ pK_{Xpyr} + 0.08\). The Leffler-Grunwald parameters \(\alpha = \beta_F / \beta_{EQ} = \frac{d \ln k_F}{d \ln k_{EQ}}\) for N-S fission \(0.8 \pm 0.05\) and S-O formation \(0.13 \pm 0.002\) were derived from data obtained by varying
the structure of the substituted pyridines and phenols. From these $\alpha$ values, Williams deduced that the controlling transition state has only weak N-S and S-O bonds and is symmetrical. If the apical bond of the stepwise intermediate (Scheme 4, path b) is assumed to be analogous to that in the tetracoordinate sulfur species, then the Brönsted plot data offered by Williams is consistent with a concerted mechanism and not with the stepwise mechanism.

If the stepwise intermediate had extraordinarily weak apical bonds, close in structure to the transition state for the rate-determining step, the data is also consistent with a stepwise mechanism.

There is precedent for such weakly bonded apical atoms. Martin and coworkers $^{19-21}$ synthesized several stable sulfuranes $^{10}$ and sulfurane oxide $^{11}$. Their trigonal bipyramidal geometries were deduced from X-ray crystallographic data. The apical S-O bonds were found to be significantly longer than the sum of the sulfur and oxygen covalent radii (1.70 Å). $^{22}$ The S-O apical bonds in sulfurane $^{10}$ were ca. 1.82 Å and in sulfurane oxide $^{11}$, ca. 1.78 Å. Bond orders for these apical S-O bonds were 0.62 and 0.74. Martin suggested that the $d$ orbitals of sulfur are not extensively involved in the apical bonding of this class of compounds.
Martin and coworkers \textsuperscript{23} synthesized an analogue of
the intermediate expected from endocyclic nucleophilic
substitution at sulfur(VI). Sulfuranilide dioxide 12
resulted from treatment of the conjugate acid 13 with
tetraethylammonium hydroxide. It was the first example of a
10-S-5 single minimum ground state anion.

The dynamic equilibrium between conjugate acids 13a
and 13b was consistent with the coalescence to a single
peak of two $^{19}$F NMR singlets with an increase in temperature. Base catalysis of the above equilibrium is postulated to go through sulfuranilide dioxide anion 12 as only one broad fluorine singlet at $\delta$ 75.2 ppm is observed. The stabilization of the anion by bridging to form the 10-S-5 sulfuranilide dioxide anion 12 would lower the energy of the equilibrium and explain the large increase in rate of equilibration when it is base catalyzed.

![Chemical Structures](image)

The pKa value at 25°C for the hypothetical equilibrium between the alcohol 13 and its conjugate base 14 was estimated using a Hammett $\sigma$ correlation, to be 9.1. The observed pKa value, measured titrimetrically, was 7.2. This lower value implies that the closed structure, 12, is more stable in solution than the open isomer 14.
An X-ray structural analysis was done on sulfuranilide dioxido anion 12. The geometry about sulfur is trigonally bipyramidal. The equatorial angles, \(<\text{cd}\) and \(<\text{de}\) are 117.8° and 122.7°, respectively. This is a very small deviation (less than 3°) from the ideal angle 120°. The apical O-S-O bond angle, \(<\text{ab}\) is 192.31° which is 12° from the ideal 180°. The apical oxygen atoms are bent away from the equatorial
The bond lengths of the equatorial S-O bonds are 1.42 Å and of the equatorial S-C bond, 1.77 Å. The apical S-O bond lengths are 1.91 Å and 1.93 Å, which is significantly longer than the sum of the sulfur and oxygen covalent radii, 1.70 Å.22

The question of a stepwise versus a concerted reaction mechanism has also been asked concerning nucleophilic substitution at phosphorus. A stepwise mechanism would involve a phosphorane intermediate analogous to the sulfurane intermediates discussed above. Phosphoranes are well-known compounds.24 Many structural analyses have been done on them. Buckwald, Pliura and Knowles25 described an example of a phosphorane intermediate in a nucleophilic substitution reaction at phosphorus. This will be discussed later in detail.

Jencks and Skoog26 observed a linear Brönsted-type relationship for phosphoryl transfer from 3-methoxypyridine to pyridines having a wide range in pKₐ. The phosphoryl transfer could go through a single transition state for a concerted mechanism, (Scheme 5, kₒ), whereas a stepwise
mechanism would involve two different transition states (Scheme 5, $k_1$ and $k_2$), and must undergo a change in rate-determining step with changing basicity of the nucleophile. The reaction coordinate diagram (Scheme 5) illustrates a change in rate-determining step in the stepwise pathway as the substituted pyridine changes from less nucleophilic (solid line) to more nucleophilic (dashed line) than 3-methoxypyridine.

![Scheme 5: Phosphoryl Transfer from 3-Methoxypyridines to Pyridines.](image)

The two transition states (a and b) would differ in the amount of bond formation and cleavage of the nucleophile and leaving group. A stepwise mechanism would show a nonlinear Brønsted-type correlation and a break at the pKa of the leaving group, 3-methoxypyridine. The Brønsted plot of log
k versus $pK_{\text{Nu}}$ was linear with a slope of $\rho_{\text{Nu}} = 0.17$. There is no evidence for a change in rate-determining step. The results are consistent with a concerted reaction mechanism in which a single, symmetrical transition state involves weak bonding to both the entering and leaving pyridines.

A similar study was done by Bourne and Williams$^{27}$ on the phosphoryl transfer from isoquinoline-$N$-phosphonate to substituted pyridines. A linear Brönsted relationship was found between the second-order rate constants and the $pK_a$ of the pyridines. This also supports a concerted mechanism.

Generally, it is assumed that the nucleophile approaches sulfur at an angle of $180^\circ$ from the leaving group. This would result in a diapical arrangement of the nucleophile and leaving group in the trigonal bipyramidal intermediate or transition state, and lead to inversion of configuration at sulfur (Scheme 6). Other approaches are possible. The nucleophile could approach sulfur at an angle of $120^\circ$ with respect to the leaving group. This would result in an equatorial-equatorial arrangement of the nucleophile and leaving group in the trigonal bipyramidal intermediate or transition state, leading to inversion of configuration at sulfur. The nucleophile could also approach the sulfur atom at an angle of $90^\circ$ with respect to the leaving group. This would result in an
apical-equatorial arrangement of the nucleophile and leaving group about sulfur and would lead to retention of configuration at sulfur. Although there are no demonstrated cases of retention of configuration in nucleophilic substitution at tetracoordinate sulfur(VI), there are examples of retention in nucleophilic substitution at tricoordinate sulfur(IV). This will be discussed later.

Scheme 6: Stereochemical Course of Nucleophilic Substitution at Tetracoordinate Sulfur(VI).

To determine whether the colinearity of the nucleophile, sulfur atom, and leaving group is necessary for nucleophilic substitution at sulfur(VI), endocyclic
substitution can be used to probe the effects of large deviations from the proposed ideal Nu-S-L angle of 180°. In endocyclic substitution, the leaving group, L, is bonded to the nucleophile, Nu, so that the atom undergoing attack, X, is transferred from the leaving group to the nucleophile intramolecularly (eq. 5). In contrast, in exocyclic substitution, the nucleophile attacks atom X intramolecularly with ring formation and the leaving group is lost from the parent molecule (eq. 6).

\[
\begin{align*}
\text{Nu} & \quad \text{X} \quad \text{Nu} - \text{X} \quad \text{(5)} \\
\text{Nu} & \quad \text{X-L} \quad \text{Nu-X+L} \quad \text{(6)}
\end{align*}
\]

Eschenmoser et al. attempted to find an example of endocyclic substitution at carbon. When sulfonate ester 15 was treated with one equivalent of sodium hydride, it rearranged to sulfone 16 (Scheme 7). If this reaction was intramolecular, and therefore a case of endocyclic substitution, then it would involve a six-membered cyclic transition state 17 where the Nu-C-L angle would be approximately 90°. Due to constraints of
the six-membered ring, the carbanion cannot attack intramolecularly $180^\circ$ away from the leaving group.

A crossover experiment was done using a mixture of the $d_0$ compound, 15, and the $d_6$ compound, 18. The mass spectrum of the product showed a $d_0 : d_3 : d_6$ ratio of 1 : 2 : 1 which is the ratio expected from an intermolecular reaction. This suggests that a $90^\circ$ angle of attack of the nucleophile on carbon doesn't occur. Since severe bond angle distortions would occur during backside attack in the six-membered cyclic transition state, the nucleophile prefers to attack intermolecularly rather than intramolecularly.

Scheme 7: A Study of Endocyclic Substitution at Carbon.
Scheme 3: Exocyclic Substitution at Carbon.

When Eschenmoser et al. synthesized an exocyclic system, where colinearity of the nucleophile, carbon, and leaving group was possible, the reaction did occur intramolecularly (Scheme 8). A crossover experiment with the analogous $d_5$ compound was run and the mass spectrum of the product showed a $d_0 : d_5$ ratio of 1:1. An intermolecular reaction would have led to a $d_0 : d_2 : d_3 : d_5$ ratio of 1:1:1:1.

King and McGarrity studied endocyclic substitution reactions at carbon. When aminosulfonate ester 19, (eq. 7) was placed in aqueous solution, a mixture of the substitution product 20 and hydrolysis product 21 resulted. When aminosulfonate ester 19 was placed in chloroform (eq. 8), substitution product 20 was formed quantitatively.
If this reaction occurred via an endocyclic pathway, it would involve an eight-membered cyclic transition state. Examination of molecular models suggest backside attack on carbon might be feasible in an eight-membered ring transition state. A crossover experiment was done using the $d_0$ compound 19 and $d_9$ compound 22 (eq. 9). The mass spectrum of the product mixture contained four peaks, a $d_0 : d_3 : d_6 : d_9$ ratio of 1 : 1 : 1 : 1. These results are in agreement with a completely intermolecular reaction.
King and McGarrity also looked at benzo-fused compounds to increase the likelihood of seeing an endocyclic process. Aminosulfonate esters 23a and 24a, were converted quantitatively into the betaines 25a and 26a, respectively (eq. 10,11).

\[
\begin{align*}
\text{23a} & \quad \rightarrow \quad \text{25a} \\
\text{24a} & \quad \rightarrow \quad \text{26a} \\
\end{align*}
\]

When the crossover experiment was carried out with 23a and its deuterated analogue (d₉) 23b, only an intermolecular reaction was observed even with concentrations as low as 5 X 10⁻⁴ molar. An equimolar mixture of 24a and 24b, however, gave betaine 26.
with a labeling pattern in accord with 16% endocyclic and 84% intermolecular reaction. The proportion of endocyclic reaction decreased with an increase in the initial concentration. There is less deviation from the ideal $180^\circ$ orientation of the nucleophile, carbon and leaving group in the nine-membered cyclic transition state arising from 24 than in the eight-membered cyclic transition state arising from 23 as confirmed by crossover experimental results.

An endocyclic system was utilized by Buckwald, Pliura and Knowles $^{25}$ to study the stereochemistry and mechanism of the acid-catalyzed 1,2-phospho group migration of 2-[(R)-$^{16}$O, $^{17}$O, $^{18}$O] phosphopropanediol (Scheme 9).

![Diagram of retention of configuration at phosphorus during endocyclic substitution.](image-url)
The reaction involves heating 27 in 0.5 N HClO₄, followed by isolation and purification of the remaining 27 and the product 28 and subjecting each to stereochemical analysis by ³¹P NMR. If the mechanism involved a free monomeric metaphosphate species, 28 would be racemized at phosphorus. The mechanism cannot involve 165° angle of approach of the nucleophile relative to the leaving group due to the constraints of the ring system. Apical approach of the entering nucleophile to form a pentacoordinate intermediate that must undergo pseudorotation to allow expulsion of the leaving group from an apical position would go with retention of configuration at phosphorus. The stereochemical analysis showed that product 28 was formed predominantly with retention as predicted by the pseudorotation mechanism (Scheme 9). Intermolecular solvolysis of monoesters of phosphoric acid proceeds with inversion as shown by the Buckwald and Knowles study of the methanolysis of phenyl (R)-[¹²⁵O, ¹⁷O, ¹⁸O] phosphate.

Würl and Lee demonstrated for the first time intramolecular nucleophilic substitution at sulfanyl sulfur via a five-membered cyclic pentacoordinate sulfur intermediate or transition state. When (R)-1-ephedrine-4-toluenesulfinyl (29) (4.1 X 10⁻³ molar) was
treated with lithium dicyclohexylamide, sulfinyl transfer occurred with predominant retention of configuration, going through an intramolecular mechanism (Scheme 10), i.e. (R)-1-ephedrine-4-toluenesulfinamide was 30% optically pure. As the concentration of sulfinate was increased, the amount of inversion increased as the likelihood of intermolecular substitution increased. When the sulfinate concentration was $8.2 \times 10^{-2}$ molar, the (S)-1-ephedrine-4-toluenesulfinamide was 66% optically pure. Some runs of this experiment afforded

$$\text{ArS(O)OCH(Ph)CH(\text{CH}_3)N(\text{CH}_3)S(\text{O})\text{Ar}, which supports the idea that inversion of configuration is due to an intermolecular pathway.}$$

An edge attack (equatorial) (Scheme 10) would result in

**Scheme 10:** Retention of Configuration at Sulfur(IV) During Endocyclic Substitution.
a trigonal bipyramidal sulfur intermediate with the oxygens in a diapical arrangement. A face attack (apical) would lead to an unfavorable trigonal bipyramidal sulfur intermediate where the electronegative OR group occupies an equatorial position (eq. 12). This trigonal bipyramidal intermediate would have to go through one pseudorotation to convert to a more stable trigonal bipyramid in which the OR group would be apical. Since this reaction goes with retention at low concentration, it is intramolecular and, therefore, the first case of endocyclic substitution at sulfur(IV).
Hellwinkel and Closson and their coworkers observed endocyclic nucleophilic substitution at sulfur(VI) in compounds having the general structure 30, where R, R' and R" were combinations of H, CH₃ and OCH₃ (eq. 13). When two equivalents of alkyl lithium (e.g., methyl lithium, butyl lithium) were added, compounds of the general structure 31 resulted in moderate to good yields. The highest yield was obtained in the rearrangement of N-methyl-N-phenyl-benzenesulfonamide (30a) to 31a (R=R"=H, R'=CH₃) in 89% yield upon treatment with two equivalents of methyl lithium in THF at 25°C for two hours (eq. 13).

\[
\begin{align*}
\text{NHR'} & \quad \text{SO}_2 \text{N} \\
R & \text{SO}_2 & \text{NHR'} \\
\text{MeLi} & \quad \rightarrow \\
R' & \text{SO}_2 & \text{NHR'} \\
\text{30} & \quad \rightarrow & \quad \text{31} \\
\end{align*}
\]

A crossover experiment was performed in which a mixture of sulfonamides 32 and 33 was treated with n-butyllithium at 25°C (eq. 14). Only the sulfones 34 and 35 were isolated. GC analysis of the reaction mixture showed the crossover products 36 and 37 to be absent.
Since no crossover products were found, it was assumed to be an intramolecular reaction. Closson postulated a mechanism which involved the formation of a dianion from the sulfonamide before rearrangement occurred (Scheme 11).

Scheme 11: Closson's Example of Endocyclic Substitution at Sulfur(VI).
Treatment of sulfonamide 38 with one equivalent of alkyllithium followed by quenching with methyl iodide yielded unrearranged ortho-methylated sulfonamide 39. This supports the first step of ortho-metalation to form 40. Treatment of sulfonamide 38 with three equivalents of methyllithium at 25°C, followed by quenching after 90 minutes with methyl iodide, led to the observed aminosulfone 41.

Closson didn't offer experimental support for the existence of dianion 42, (Scheme 11), but postulated its formation based on the following facts: (1) it is the ortho position to which the sulfonyl group migrates; (2) if these ortho positions are blocked by methyl groups, rearrangement doesn't occur; (3) chelation of the lithium cation by one of the sulfonyl oxygens via a six-membered ring is feasible.

Hellwinkel and Supp 36 rearranged \( N, N, N', N' \)-tetraphenylsulfonamide (43)
with four equivalents of n-butyllithium and found that it rearranged to \( N,N \)-diphenyl-2-\((N'\text{-phenyl-}
\text{amino})-\text{benzenesulfonamide} \) (44) (eq. 15). None of the analogous rearranged product 45 was detected.

\[
\begin{align*}
\text{Ph} & \quad \text{NSO}_2\text{NPh}_2 \\
\text{43} & \quad \text{n-BuLi} \\
\text{NHPh} & \quad \text{SO}_2\text{NPh}_2 \\
\text{44} & \\
\text{NHPh} & \quad \text{SO}_2\text{NPh}_2 \\
\text{45} & \\
\end{align*}
\]

(15)

Hellwinkel and Supp 37 observed the rearrangement of cyclic sulfonamides 46b to dibenzo[\(b,f\)] [1,4] thiazepine dioxides 47b upon the addition of at least two equivalents of n-butyllithium (eq. 16 and Scheme 12).

\[
\begin{align*}
\text{R} & \quad \text{R'} \\
\text{46} & \\
\text{BuLi} & \\
\text{47} & \\
\end{align*}
\]

(16)

\[
\begin{align*}
\text{R} & \quad \text{R'} & \text{yield} \\
a & \text{H} & \text{Me} & 95\% \\
b & \text{Me} & \text{Me} & 90\% \\
c & \text{Me} & \text{Ph} & 37\% \\
\end{align*}
\]

A mechanism similar to Closson's was proposed (Scheme 12). When compounds 46a-c were treated with only one
equivalent of \textit{n}-butyllithium at -70°C, monometalation occurred ortho to the sulfonyl group. The carbanion 48 was persistent, indicating that the N-aryl group was now in a position too far away for intramolecular transmetalation. When a second equivalent of \textit{n}-butyllithium was added the rearranged product 47a-c was isolated in yields of 37\% to 95\% after hydrolysis. It is not known whether structure 50 is an intermediate or transition state.

\[
\begin{align*}
\text{BuLi} & \quad \text{BuLi} \\
\text{SO}_2 & \quad \text{Li} \\
\text{BuLi} & \quad \text{BuLi} \\
\text{Li} & \quad \text{Li} \\
\text{SO}_2 & \quad \text{Li} \\
\text{Li} & \quad \text{Li} \\
\end{align*}
\]

\[ R, R', R'' = \text{H, Me, OMe} \]

Scheme 12: Hellwinkel's Example of Endocyclic Substitution at Sulfur(VI).

If the carbanion 51 (Scheme 13) underwent apical attack at sulfur, sulfurane 52 would result where the nitrogen and the two oxygens are equatorial. This assumes 52 is an intermediate rather than a transition state.
Intermediate 52 could pseudorotate to either sulfurane 53 or 54 to put the nitrogen leaving group in an apical position. The ring could open up from this position as the leaving group could leave apically (principle of microscopic reversibility). This would lead to retention of configuration at sulfur as seen in product 55.

Scheme 13: Apical or Equatorial Attack at Sulfur(VI) in Hellwinkel's Example of Endocyclic Substitution.

If the carbanion 51 underwent equatorial attack at sulfur, sulfurane 56 would result. In this structure both the leaving group, nitrogen, and the nucleophilic
carbon are equatorial. However, 56 would be a very distorted trigonal bipyramid and perhaps would better be described as a square pyramid. In order for the nitrogen to leave equatorially and the ring open to form the product, 57, the sulfonyl oxygens would have to bend toward the center of the ring. This is stereochemically impossible and the product 57, an example of inversion of configuration at sulfur(VI), would not be expected to form. Therefore, the only path for endocyclic substitution of 51 would be apical attack of the carbanion on sulfur(VI).

Hellwinkel and coworkers 38 studied the synthetic potential of this intramolecular rearrangement as a means of creating new seven-membered heterocycles from five-membered heterocycles. They replaced the CR'2 group with a carbonyl group to see how unsaturation affected the reaction. As a probe, the N-benzoyl-N-tosyl-toluidide 59 was treated with n-butyllithium at low temperature; the benzoyl group migrated to the phenyl ring to form 60 (eq. 17).

\[
\begin{array}{c}
\text{CH}_3 \quad \text{N} \quad \text{SO}_2\text{Ar} \\
\text{Br} \quad \text{COAr} \\
\text{59} \\
\end{array} \xrightarrow{t.\text{BuLi}} \quad \begin{array}{c}
\text{CH}_3 \quad \text{N} \quad \text{HSO}_2\text{Ar} \\
\text{COAr} \\
\text{60} \\
\end{array}
\]

\[(17)\]

Intramolecular nucleophilic attack occurred on sulfur
in the reaction of 1,2-benzisothiazolone-1,1-dioxide 61
with n-butyllithium at low temperature, followed by
warming to room temperature and hydrolysis to form
dibenzo[b,f][1,4]thiazepin derivative 62 (eq. 18).

\[
\text{CH}_3
\]

Carbanion 63 cannot approach the carbonyl carbon
from the preferred angle of attack (110° with the
carbonyl bond), but it is in a position to attack the sulfur
atom to form a trigonal bipyramidal sulfur center (eq. 19).

\[
\text{CH}_3
\]

Hellwinkel\textsuperscript{38} also subjected (N-phenyl)
6H-dibenzo[c,e]-[1,2]thiazin-5,5-dioxide (64) to
n-butyllithium at low temperature and observed the
rearranged product, 14H-tribenzo[b,e,g][1,4]thiazocin
9,9-dioxide (65). The question is still unanswered.
whether 66 is an intermediate or transition state.

\[
\begin{align*}
\text{64} & \xrightarrow{1.\text{BuLi}} \text{65} \\
\text{65} & \xrightarrow{2.\text{H}_2\text{O}} \text{66}
\end{align*}
\]

Hellwinkel et al. \textsuperscript{39,40} explored the generality of this rearrangement using other groups, U, and various leaving groups, E (eq. 21).

\[
\begin{align*}
\text{E} & \text{U} \\
\text{NR} & \text{COR} \\
\text{POAr}_2 & \\
\text{SiR}_3 & \\
\text{O} & \text{COR}
\end{align*}
\]

Hellwinkel and Lenz \textsuperscript{41} further explored the rearrangement of sulfonamides (Scheme 14). \textit{N}-naphthyl-\textit{N}-methyl-4-toluene sulfonamide (67) rearranged to aminosulfone 68 in 80% yield upon treatment with one equivalent of \textit{n}-butyllithium. The mechanism involves metallation ortho to the sulfonyl group followed by transmetalation and rearrangement. When the analogous sulfonamide 69 was treated with \textit{n}-butyllithium, only 12% of the rearranged sulfone 70 was observed (Scheme 14).
Scheme 14: Endocyclic Substitution at Sulfur(VI) to Different Ortho Positions with Naphthalene Systems.

When the N-(2-biphenyl)sulfonamide 71 was treated with n-butyllithium or t-butyllithium, it rearranged to sulfone 72 in 10% and 41% yield, respectively (Scheme 15). Formation of the product was explained by initial halogen-metal exchange to form 73 which was followed by transmetallation to 74 and then to 75. Finally, 75 rearranged to the product 72.
Scheme 15: Endocyclic Substitution at Sulfur(VI) with Iodo-biphenyl Systems.

An interesting example from Hellwinkel and Lenz's work is the reaction of sulfonamide 76 (Scheme 16). It seemed feasible that sulfonamide 76 when treated with n-butyllithium could rearrange to sulfone 77. When the reaction was carried out, no 77 was observed but 18-23% of 78 was obtained. Hellwinkel proposed the following mechanism to explain the formation of the products (Scheme 16).
After deprotonation of the benzyl carbon by n-butyllithium, the anion 79 can eliminate benzenesulfinate anion to form the quinoid structure 80. Anion 79 could also cyclize to form the resonance-stabilized anion 81. Intermediate 80 could react with anion 81 to form a new adduct 82. Attack of the nitrogen anion on the ring would form compound...
which after protonation would yield product 78.

Engberts et al.\textsuperscript{42} recently reported an example of endocyclic substitution at sulfur(VI), the hydrolysis of the benzensulfonamide 84 where the nucleophile is a neighboring hydroxyl group (eq. 22). The reaction is specific acid catalyzed and very fast; the kinetics were followed by the stopped-flow technique. Engberts and coworkers offered no evidence to support or rule out a pentacoordinate sulfur intermediate in this case. They compared the rate of hydrolysis of 84 to that of the exocyclic benzenesulfonamide 85.

![Diagram of chemical structures]

Sulfonamide 85 (R=H) remained unchanged after seven months at 25°C in aqueous ethanol containing 1M HCl. The half life of 85 (R=Me) was about twenty minutes under the same conditions. Sulfonamide 84 (R=Me) was
about 4000 times more reactive than the latter. This large increase in reactivity when a geminal dimethyl group is present was explained by the observation that gem-dialkyl substitution generally provides a powerful driving force for the formation of small rings. The rate of hydrolysis of 84 (R=Me) was compared to the hydrolysis of 86 (in 70% v/v CF$_3$CO$_2$H-H$_2$O at 99°C). The half life of 86 (R=H) was 167 hours. When R=Me, the half life was decreased by a factor of 100. These reactions were very slow compared to the intramolecular reaction of 84 (R=Me). Engberts suggested that the enthalpy barrier in 84 involved in the positioning of the hydroxyl group for effective nucleophilic attack on the sulfur(VI) atom is already partly overcome in the initial state.

The 4000-fold greater rate of 84 (R=Me) relative to 85 (R=Me) was interesting because when the rates of hydrolysis of 87 and 88 were compared,
was more reactive by a factor of 15. The hydrolyses of 87 and 88 involve nucleophilic attack of the carboxyl oxygen on sulfur with loss of the nitrogen to form the mixed anhydride $\text{C}(\text{O})\text{OSO}_2^-$, followed by hydrolysis of the anhydride to form the carboxylic and sulfonic acids. Engberts suggested that the rate-determining step of the hydrolysis of 87 is the nucleophilic attack of the carboxyl group on sulfur(VI) whereas with 88, it is the hydrolysis of the mixed anhydride. The factor of 4100 in the reaction of 84 ($R=\text{Me}$) compared to 85 represents the difference in reactivity of the sulfonamide groups as they both have the same rate-determining step.

An example of an apparent endocyclic substitution at sulfur(VI) was reported by Andersen et al. 2-Aminophenyl 4-toluenesulfonate (89) was prepared by selective $\text{O}$-sulfonation of o-aminophenol using 4-toluenesulfonyl chloride and triethylamine. When treated with $n$-butyllithium, 89 was found to rearrange to sulfonamide 90 (eq. 23). Sulfonamide 90 was prepared by selective $\text{N}$-sulfamation of o-aminophenol with 4-toluenesulfonyl chloride and pyridine. When 90 was treated with $n$-butyllithium, no sulfonate 89 was detected. Therefore, the reaction is not reversible.
The generality of this reaction (eq. 23) was explored with various substituents on the benzene rings. All were found to rearrange. A methyl group on the nitrogen didn't prevent the reaction from occurring since 2-(methylamino)phenyl 4-toluenesulfonate rearranged to the corresponding sulfonamide. A crossover experiment indicated the reaction to be intramolecular; this will be discussed later in detail.

Even though the reaction is intramolecular, there is an alternative mechanism which explains the formation of product. This involves a base-induced 1,4-elimination to form o-quinonimine 91 and 4-toluenesulfinate anion (eq. 24). The ion-molecule pair could recombine in a solvent
cage to yield the observed sulfonamide. Addition of arylsulfinic acids to N,N-alkylquinone diimides has been reported. 44

This elimination-addition mechanism was suspected to be involved due to the isolation of 2,2'-dihydroxy-5,5'-dimethylazobenzene (92) from the reaction of 93 with n-butyllithium (Scheme 17). 43 Azobenzene 92 might arise by a base-induced 1,4-elimination with consequent formation of an o-quinonimine 94 followed by attack of another nitrogen anion to form 95. A second base-induced 1,4-elimination to 96 followed by deprotonation of the nitrogen would lead to azobenzene 92.

Scheme 17: Mechanism of 1,4-Elimination-Addition of 2-Aminoaryl Arenesulfonates.
RESULTS AND DISCUSSION

The purpose of this research was to investigate the effect of geometry on nucleophilic substitution at sulfur(VI) by utilizing molecules having the potential to react endocyclically.

The general process is illustrated by the structure shown below where X is S(VI). In endocyclic substitution, the nucleophilic atom (Nu) and the leaving group atom (L) are attached to one another. Thus, the intermediate or transition state formed as the nucleophile bonds to sulfur is cyclic. By varying the structural connection between the nucleophile and the leaving group, the angle of approach of the nucleophile to the sulfur atom with respect to the sulfur-leaving group bond can be modified. If substitution at sulfur(VI) proceeds via a trigonally bipyramidal intermediate or transition state, then three limiting cases may be envisaged: (1) the nucleophile and leaving group will both be apical (180°), (2) they both will be equatorial (120°), or (3) one will be apical and the other equatorial (90°). By restricting the number of atoms connecting the nucleophile and the leaving group, the di-apical or 180° pathway will be eliminated if the reaction is intramolecular. Since inversion of configuration is expected in the diequatorial or 120°
case whereas retention is expected in the apical-equatorial or 90° case, information about any intermediate or transition state may be forthcoming through a study of the stereochemistry at sulfur for an intramolecular example.

\[
\begin{align*}
&\text{L} - X \\
&\text{n} \\
&\text{Nu}
\end{align*}
\]

This thesis research was restricted to a search for examples of endocyclic substitution at sulfur(VI). Several substrate molecules were prepared. They were treated with strong bases, n-butyllithium or lithium diisopropylamide, in order to deprotonate a nitrogen or carbon atom in the molecule. It was hoped the conjugate base of the nitrogen or carbon would function as a nucleophile and attack a sulfonyl sulfur atom intramolecularly with displacement of a leaving group from the latter. In several cases, the desired substitution process was observed. Appropriately deuterium-labeled substrates were prepared and crossover experiments were run to determine whether or not these reactions were intramolecular. In two cases they were - one involving a four- and the other a five-membered cyclic intermediate or transition state. In a third case, the substitution reaction was shown to be intermolecular. These and related reactions will be discussed. No stereochemical
investigations were undertaken.

To simplify the discussion, trigonally bipyramidal structures which are intermediates rather than transition states will be assumed unless otherwise specified.

In order to continue the original studies by Andersen et al.,43 the substitution reaction of 2-aminoaryl arenesulfonates, 2'-aminophenyl 3-trifluoromethylbenzenesulfonate (97) was synthesized from 2-aminophenol and 3-trifluoromethylbenzenesulfonyl chloride (98) (eq. 25). The sulfonyl chloride 98 was prepared by sulfonation of trifluoromethylbenzene with oleum followed by treatment of the salt with phosphorus pentachloride. If 97 underwent endocyclic substitution upon treatment with strong base, it would be expected to form N-(2'-hydroxyphenyl)-3-trifluoromethylphenylsulfonamide (99) via a five-membered ring intermediate.
When 97 was treated with four equivalents of n-butyllithium in THF at 0°C, a black tar resulted. TLC showed twelve spots. No further work was done on this reaction. When 97 was treated with three equivalents of lithium diisopropylamide (LDA) in THF at -78°C, 99 was isolated in 25% yield (eq. 26). Sulfonamide 99 was synthesized by selective N-sulfonation using pyridine and sulfonyl chloride 98. The melting point and spectra of the sulfonamide obtained from the rearrangement matched those of the synthesized sulfonamide.
To investigate the generality of this reaction, 3'-(2'-amino)pyridyl 3-trifluoromethylbenzenesulfonate (100) was prepared from sulfonyl chloride 98 and 2-amino-3-hydroxypyridine. When this sulfonate was treated with three equivalents of LDA in THF at -78°C, it rearranged to the expected sulfonamide 101 in 52% yield (eq. 27) and starting material was recovered in 13% yield. Attempted synthesis of 101 failed, but the sulfonamide isolated from the rearrangement gave a satisfactory C, H, and N analysis as well as appropriate spectral data.

\[
\begin{align*}
\text{LDA} & \quad \rightarrow \\
100 & \quad \rightarrow \\
101 & \quad (27)
\end{align*}
\]

2-Trifluoromethylbenzenesulfonyl chloride (102) was prepared from 2-trifluoromethylaniline by diazotization, sulfonation with SO₂ and chlorination. The sulfonyl chloride 102 was coupled with 2-amino-3-hydroxypyridine to prepare 3'-(2'-amino)pyridyl 2-trifluoromethylbenzenesulfonate (103). When sulfonate 103 was treated with three equivalents of n-butyllithium, it rearranged to N-2'-'[(3'-hydroxy)pyridyl]-2-trifluoro-
methylbenzenesulfonamide (104) in 51\% yield (eq. 28).

\[ \begin{align*}
103 \quad \text{LDA} \quad & \quad 104 \\
\end{align*} \]

Thus the sulfonate esters 97, 100 and 103 all underwent the rearrangement to form the corresponding sulfonamides 99, 101 and 104. If these reactions are examples of endocyclic substitution, they would involve five-membered cyclic intermediates with a nitrogen as the nucleophile and a phenolic oxygen as the leaving group. Yildiz \(^7\) did a crossover experiment to determine if the rearrangement of 2-aryl arenesulfonates is intramolecular (and therefore, endocyclic), or intermolecular. If sulfonates 105 and 106 were treated with strong base, only sulfonamides 107 and 108 should be observed if the reaction was intramolecular (eq. 29). If the reaction were intermolecular, all four sulfonamides, 107, 108, 109 and 110, should be observed. Equal amounts of 105 and 106 were treated with four equivalents of \(n\)-butyllithium in THF. Comparison of the proton NMR
spectra of the reaction products with the spectra of the synthesized sulfonamides indicated that only 107 and 108 were formed; sulfonamides 109 and 110 were not observed. Therefore, it was concluded that the reaction was intramolecular and a case of endocyclic substitution at sulfur(VI). This conclusion is based on the assumption that the rearrangement of sulfonates 105 and 106 proceed at the same rates.

However if one sulfonate rearranged at a faster rate than the other sulfonate, it would be possible for the faster reacting sulfonate to react intermolecularly to completion before the slower reacting sulfonate had reacted
very much. In this case, only the "intramolecular" products would be observed even though the reaction proceeded via an intermolecular pathway.

To ascertain whether the rearrangement of 2-aminoaryl arenesulfonates is indeed intramolecular, a new crossover reaction was designed using deuterium-labeled substrates. There should be little or no rate difference between the substrate and its deuterated analog. 2'-Methylamino-phenyl 4-toluenesulfonate (111) had been synthesized and rearranged by McGraw,\textsuperscript{46} using four equivalents of \text{n}-butyllithium in THF. A 43\% crude yield of N-methyl-N-(2'-hydroxy)phenyl-4-toluenesulfonamide (112) was obtained (eq. 30). The synthesis of 111 involved selective O-tosylation with 4-toluenesulfonyl chloride and triethylamine at room temperature (55\% yield) followed by N-methylation by treatment with potassium hydroxide and dimethyl sulfate (22\% yield). It was decided to use this reaction for the crossover study and another method to synthesize 111 was investigated to improve the yield so that the deuterated analog 113 could be prepared in a reasonable yield.

\begin{equation}
\begin{array}{c}
\text{OSO}_2\text{ToI} \\
\text{NHCH}_3
\end{array}
\begin{array}{c}
\rightarrow
\end{array}
\begin{array}{c}
\text{OH} \\
\text{NSO}_2\text{ToI}
\end{array}
\begin{array}{c}
\text{CH}_3
\end{array}
\end{equation}

\textbf{111} \quad \textbf{112}
O-Tosylation of 2-aminophenol in methylene chloride at -78°C resulted in 81% yield of 2'-aminophenyl 4-toluenesulfonate (114) (Scheme 18). Krishnamurthy's procedure of N-monomethylation by reduction of a formamide was applied. 2'-Formamidophenyl 4-toluenesulfonate (115) was prepared in 80% yield by formylating 114 with acetic formic anhydride prepared in situ from acetic anhydride and formic acid. Reduction of formamide 115 by lithium aluminum hydride gave 21% sulfonate 111 and 70% sulfonamide 112. Apparently sulfonate 111 rearranged to sulfonamide 112. Reduction of formamide 115 with borane:dimethylsulfide complex resulted in 74% of 111 (Scheme 18).
Scheme 18: Synthesis of Sulfonate 111.

Rearrangement of sulfonate 111 with LDA was investigated to see if the yield of sulfonamide 112 could be improved. LDA is a hindered strong base and does not readily act as a nucleophile due to its bulky isopropyl groups. When sulfonate 111 was treated with three equivalents of LDA in THF at -78°C, sulfonamide 112 was isolated in 5% yield and recovered starting material in 81% yield. When the reaction was performed at room temperature, sulfonamide 112 was isolated in 44% yield. This agrees with McGraw's result for the treatment of sulfonate 111 with n-butyllithium in THF at room temperature which gave a 43% crude yield of 112.
The deuterated sulfonyl chloride 116 was prepared in 63% yield by chlorosulfonation of d₈-toluene (Aldrich) with chlorosulfonic acid (eq. 31). The mass spectrum of this compound showed isotopomers having one to four protons to be present in significant amounts (Table 1). The d₅ and d₆ compounds were the most abundant and of very nearly the same intensity. The proton NMR of the d₈-toluene indicated that it had an insignificant amount of proton isotopomers (the spectrum amplitude was set at 2000 and residual aromatic protons were barely visible). It is possible that the proton impurities developed during the quenching of the chlorosulfonation reaction with crushed ice. The four aromatic deuterons could have exchanged as strong acid and water were present. The d₃-methyl group would not have exchanged and the mass spectrum supports this as only isotopomers having one to four protons are observed. The deuterated sulfonyl chloride 116 was coupled to 2-aminophenol to prepare sulfonate 117 (eq. 31). The mass spectrum of this compound showed the same ratio of proton isotopomers as 116.
Table 1: Mass Spectrum of d\(_7\)-Toluene-sulfonyl Chloride (116).

<table>
<thead>
<tr>
<th>(M) (intensity)</th>
<th>(\text{H}_0)</th>
<th>(\text{d}_7)</th>
<th>197 (60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\text{H}_1)</td>
<td>(\text{d}_6)</td>
<td>196 (93)</td>
</tr>
<tr>
<td></td>
<td>(\text{H}_2)</td>
<td>(\text{d}_5)</td>
<td>195 (107)</td>
</tr>
<tr>
<td></td>
<td>(\text{H}_3)</td>
<td>(\text{d}_4)</td>
<td>194 (78)</td>
</tr>
<tr>
<td></td>
<td>(\text{H}_4)</td>
<td>(\text{d}_3)</td>
<td>193 (21)</td>
</tr>
</tbody>
</table>

Table 2: Mass Spectrum of d\(_3\)-Toluene (118).

<table>
<thead>
<tr>
<th>(M) (intensity)</th>
<th>(\text{H}_0)</th>
<th>(\text{d}_3)</th>
<th>95 (1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\text{H}_1)</td>
<td>(\text{d}_2)</td>
<td>94 (846)</td>
</tr>
<tr>
<td></td>
<td>(\text{H}_2)</td>
<td>(\text{d}_1)</td>
<td>93 (656)</td>
</tr>
<tr>
<td></td>
<td>(\text{H}_3)</td>
<td>(\text{d}_0)</td>
<td>92 (214)</td>
</tr>
</tbody>
</table>

To avoid the problem of the exchangable aromatic deuterons, d\(_3\)-methylbenzene (118) was synthesized by reducing benzotrichloride with zinc and acetic acid-d\(_4\) (Scheme 19).\(^{49}\) The acetic acid d\(_4\) was prepared by the hydrolysis of acetyl chloride with deuterium oxide. Analysis of the mass spectrum of 118 showed significant proton isotopomers. However, the molecular ion (m/e 95) gave the highest intensity and this could be monitored during the following reactions (Table 2).
Scheme 19: Synthesis of Sulfonate 122.

The d$_3$-toluene was chlorosulfonated with chlorosulfonic acid to prepare 119 which was coupled to 2-aminophenol to give sulfonate 120. Sulfonate 120 was formylated with acetic formic-d$_1$ anhydride (prepared from acetic anhydride and d$_2$-formic acid) and then reduced with d$_3$-borane:THF complex to afford the sulfonate 122 (Scheme 19). Because the d$_3$-borane:THF solution was an old sample, a trial reduction of the nondeuterated formamide 115 was carried out to observe the resulting deuterium ratio. The product sulfonate 123 showed a significant amount of proton isotopomers. The concentration of the d$_3$-borane was calculated to be 0.43 molar from the $^{11}$B NMR spectrum. The deuterated borane solution was used to reduce formamide 121. The mass spectrum of sulfonate 122 (Table 3)
showed the d$_5$ peak to be the most abundant one.

![Chemical structure](image)

Table 3: Mass Spectrum of (2'-d$_2$-Methylamino)phenyl 4-d$_3$-Methylbenzenesulfonate (122).

| M (intensity) | (H$_2$) d$_6$ 283 (51) | (H$_1$) d$_5$ 282 (67) | (H$_2$) d$_4$ 281 (32) | (H$_3$) d$_3$ 280 (11) |

A crossover experiment was performed with sulfonates 111 and 122. If the reaction was intramolecular, only 124 and 125 should be observed (eq. 32). The mass spectrum of the intramolecular product would ideally show a d$_0$ : d$_3$ : d$_6$ ratio of 1 : 0 : 1. If the reaction was intermolecular, all four sulfonamides 124-127 should be observed. The product ratio in this case ideally would show a d$_0$ : d$_3$ : d$_6$ ratio of 1 : 2 : 1. Due to the fact that 122 has significant proton isotopomers, its ratio of proton/deuteron must be taken into account when analyzing the mass spectrum of the product.
(32)

122

124

125

126

127

128
Table 4: Analysis of the Mass Spectrum of the Product of the Crossover Reaction of 111 and 122.

<table>
<thead>
<tr>
<th>m/e</th>
<th>283</th>
<th>282</th>
<th>281</th>
<th>280</th>
<th>279</th>
<th>278</th>
<th>277</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>d6</td>
<td>d5</td>
<td>d4</td>
<td>d3</td>
<td>d2</td>
<td>d3</td>
<td>d0</td>
</tr>
<tr>
<td>obs. % intensity of 111</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>14</td>
<td>83</td>
</tr>
<tr>
<td>obs. % intensity of 122</td>
<td>32</td>
<td>42</td>
<td>20</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>obs. % intensity of 128</td>
<td>17</td>
<td>22</td>
<td>12</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>calcd. % intensity (intramolecular)</td>
<td>16</td>
<td>21</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>calcd. % intensity (intermolecular)</td>
<td>5</td>
<td>9</td>
<td>6</td>
<td>27</td>
<td>18</td>
<td>8</td>
<td>27</td>
</tr>
</tbody>
</table>

Equimolar amounts of 111 and 122 were treated with three equivalents of LDA in THF at room temperature. The mass spectrum of the resulting sulfonamide revealed the ratio of deuterium to be in accord with an intramolecular process (Table 4). The percent intensities of an intramolecular reaction were calculated based on the assumption that one-half of the product sulfonamide 128 would have the same deuterium pattern as sulfonate 122 and one-half would have the same M, M+1 and M+2 pattern as sulfonate 111. The percent intensities expected for an intermolecular reaction were calculated based on the assumption that the d₀ substrate has an equal probability of reacting with another d₀ molecule or a
d₆ molecule. The same can be said for the d₆ substrate. The nitrogen nucleophile and sulfur atom are each marked with a CD₃ group. The one to three proton isotopomers of each of these methyl groups would carry over to the respective products. The deuterium pattern of each CD₃ group was considered in the calculations based on the d₃ to d₀ peaks of the respective fragments in the mass spectrum of 122 (Table 5).

Table 5: Fragments in the Mass Spectrum of 122.

<table>
<thead>
<tr>
<th>m/e (intensity)</th>
<th>d₃</th>
<th>d₂</th>
<th>d₁</th>
<th>d₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 (37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>124 (46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>123 (16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>122 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>94 (58)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93 (21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>92 (14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>91 (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The percent intensities of the d₆ to d₀ peaks of the product sulfonamide 128 from the crossover reaction matched those calculated for an intramolecular process within two percent on the average (Table 4). Therefore, it is concluded that the rearrangements of 2-aminoaryl arenesulfonates to the corresponding sulfonamides are intramolecular. This result supports the
assumption that the sulfonates used in the crossover reaction by Yildiz\textsuperscript{43} proceed at very similar rates. It is not possible, however, to declare these rearrangements to be cases of endocyclic substitution even though they are intramolecular because there is an alternative mechanism, one of elimination followed by addition (eq. 24 and Scheme 17).

To investigate this possible elimination-addition mechanism, 2'-(8'-amino)naphthyl 4-toluenesulfonate (129) was synthesized from 8-amino-2-naphthol and 4-toluenesulfonyl chloride. From examination of molecular models, the amino group appears to be too far away from the sulfur atom to undergo endocyclic substitution. However, the molecule would allow the elimination-addition mechanism or an intermolecular reaction to take place. The initially formed anion 130 could eliminate 4-toluenesulfinate anion to form the quinonimine 131. Addition of the 4-toluenesulfinate anion at nitrogen would form the rearranged product 132 (Scheme 20). When 129 was treated with three equivalents of \textit{n}-butyllithium in THF at -78\textdegree C, sulfonamide 132 was isolated in 78\% yield. This indicates that, at least in this particular case, either the elimination-addition mechanism or intermolecular substitution is probably operative.
Scheme 20: Rearrangement of Sulfonate 129.

To avoid the problem of the possible elimination-addition pathway, compounds were synthesized which appeared capable of endocyclic substitution but which lacked the o-aminophenol group. \( \text{N-Methyl-} \ N-[\text{(2'-methylsulfonyl)phenyl}] \text{4-toluenesulfonate 133} \) was synthesized (Scheme 21). The synthesis involved methylation of 2-aminothiophenol with the selective methylating agent 134 to form 135.\(^{51}\) 2-Aminothioanisole (135) was sulfonated with 4-toluenesulfonyl chloride to prepare 136 which was methylated to form sulfonamide 137. Oxidation with hydrogen peroxide in glacial acetic acid produced the sulfone sulfonamide 133. It was hoped that sodium hydride would deprotonate the sulfone methyl to create carbanion 138 (eq. 33). The carbanion could then attack
sulfur intramolecularly to form 139 and, after protonation, yield the disulfone 140. This would involve a six-membered cyclic sulfurane intermediate, a carbon nucleophile and a nitrogen leaving group.

Scheme 21: Synthesis of Sulfonamide 133.

Sulfone 141 was synthesized from 2-aminothioanisole (135) by protection of the nitrogen by acetylation, oxidation of the sulfide with hydrogen peroxide, deprotection of the nitrogen with potassium hydroxide in ethanol followed by N-monomethylation using Krishnamurthy's method\(^7\) (eq. 34).
When 133 was treated with sodium hydride in THF at room temperature, only starting material was recovered (68%). Treatment with sodium hydride in 1,2-dimethoxyethane (DME) at 10°C similarly gave only starting material. When the reaction was run at room temperature, 80% of the starting material was recovered together with 13% of 2-(methylamino)phenyl methyl sulfone (141) (eq. 35). The melting point and spectra of the isolated sulfone 141 matched those of synthetic 141. Treatment of 133 with sodium hydride in DME at 85°C gave 62% starting material and a negligible amount of sulfone 141. With n-butyllithium in THF at room temperature, a tarry reaction mixture was obtained; again starting material and sulfone 141 were isolated this time in 35% and 10% yields, respectively. When LDA in THF was used as the base at room temperature, starting material was recovered in 11% yield and sulfone 141 formed in 42% yield. A white salt was filtered from the reaction mixture and dried under vacuum. The proton NMR of the salt matched
that of an authentic sample of sodium 4-toluensulfinate and not that of sodium 4-toluenesulfonate. The yield of lithium sulfinate was 30.1%.

Thus whether the base was sodium hydride, n-butyllithium or LDA, starting material and sulfone 141 were isolated from the reaction mixture. A possible explanation for the formation of the products (141 and lithium 4-toluenesulfinate) involves deprotonation to form anion 145 followed by elimination of 4-toluenesulfinic anion to form the imine 146 (eq. 36). Hydride attack at the imine carbon would result in sulfone 141.
Sulfonate 147 was investigated to see whether it could lead to an example of endocyclic substitution via a six-membered cyclic intermediate. The synthesis of 147 involved sulfonation of salicylaldehyde followed by imine formation with methylamine (eq. 37). The imine 149 was reduced with sodium borohydride to form 147.

\[
\begin{align*}
148 & \rightarrow 149 & \rightarrow 147 \\
 & \text{CH}_2\text{CH}_2\text{NH} & \\
\end{align*}
\]

(37)

It was hoped that the nitrogen anion formed by deprotonation with base would attack the sulfur atom to form a six-membered cyclic sulfurane 150, followed by departure of the phenolic oxygen to give 151 (eq. 38). An apical-equatorial arrangement of the nucleophile and leaving group of sulfurane 150 would result from a 90° approach of the nucleophile to sulfur. The other possible sulfurane (not shown), would result from a 120° approach, would have the nitrogen and phenolic oxygen in a diequatorial arrangement.
Sulfonate 147 was treated with four equivalents of n-butyllithium in THF at -78°C. An attempt was made to separate the components of the reaction mixture by preparative plate chromatography. Five bands were obtained; TLC of each of the bands exhibited from two to seven spots. No further work was done on this reaction mixture. When 147 was treated with three equivalents of LDA in THF at -78°C, sulfonamide 151 was isolated in 33% yield. A satisfactory analysis of the product was obtained. When 147 was treated with LDA at room temperature, 151 was isolated in 40% yield.

A competition experiment with an external nucleophile
was carried out. Equimolar amounts of 147 and benzylamine were treated with three equivalents of LDA. The rearrangement product 151 was isolated in 24% yield along with a 21% yield of N-benzyl-4-toluenesulfonamide (152) (eq. 39). Although the isolation of 152 is not proof that the substitution reaction of 147 is intermolecular, this was suspected to be the case. Therefore, a crossover experiment was carried out to determine if the reaction is intermolecular.

\[ \text{147} \xrightarrow{\text{LDA}} \text{151} \]

\[ \text{152} \]

A crossover experiment was designed using 147 and its deuterated analog, 153. The synthesis of sulfonate 153 parallels that of 147. Salicylaldehyde was sulfonated with \( d_3 \)-methylbenzenesulfonyl chloride (113) to prepare 154 (eq. 40). Imine formation with methylamine to form 155 was followed by reduction with
sodium borodeuteride (Aldrich) to form 153.

\[
\begin{align*}
\text{CHO} & \quad \text{CH=NCH}_3 \\
\text{CD}_3\text{C}_6\text{H}_4\text{SO}_2 & \quad \text{CD}_3\text{C}_6\text{H}_4\text{SO}_2 \\
154 & \quad 155 & \quad 153
\end{align*}
\]

If the crossover reaction of a mixture of 147 and 153 were intramolecular, only the sulfonamides 155 and 156 would be observed (eq. 41). The mass spectrum of the intramolecular product ideally would show a \( d_0 : d_1 : d_3 : d_4 \) ratio of 1 : 0 : 0 : 1. If the reaction is intermolecular, then the four sulfonamides 155 to 158 would be obtained. In this case the \( d_0 : d_1 : d_3 : d_4 \) ratio would be 1 : 1 : 1 : 1.
When equimolar amounts of 147 and 153 were treated with three equivalents of LDA, the rearranged product 159 was isolated and analyzed by mass spectrometry. The percent deuterium in the product was in accord with a completely intermolecular reaction (Table 6).
Table 6: Analysis of the Mass Spectrum of the Product of the Crossover Reaction of 147 and 153.

<table>
<thead>
<tr>
<th>m/e</th>
<th>295</th>
<th>294</th>
<th>293</th>
<th>292</th>
<th>291</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>d4</td>
<td>d3</td>
<td>d2</td>
<td>d1</td>
<td>d0</td>
</tr>
<tr>
<td>obs. % intensity of 147</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>obs. % intensity of 153</td>
<td>51</td>
<td>29</td>
<td>15</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>obs. % intensity of 159</td>
<td>19</td>
<td>24</td>
<td>12</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>calcd. % intensity (intramolecular)</td>
<td>25</td>
<td>15</td>
<td>8</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>calcd. % intensity (intermolecular)</td>
<td>14</td>
<td>25</td>
<td>8</td>
<td>23</td>
<td>30</td>
</tr>
</tbody>
</table>

The percent intensities resulting from an intramolecular reaction were calculated based on the assumption that the resulting sulfonamide 159 would exhibit the same pattern of deuterium label as in the starting material. The product would consist of one-half fully labeled sulfonamide and one-half unlabeled sulfonamide. The percent intensities resulting from an intermolecular reaction were calculated based on the assumption that the d1-labeled nitrogen nucleophile has an equal probability of reacting with a d0 or d3-labeled sulfonyl group. The same can be said for the d0-labeled amine group. The mono-proton isotopomer of
the CHD-labeled nitrogen and the mono- to tri-proton isotopomers of the CD$_3$-labeled sulfonyl group would carry over to the respective products. The deuterium pattern for the CHD group was based on a fragment in the mass spectrum from 153 (Table 7). The CD$_3$ group deuterium pattern was taken from the mass spectrum of a predecessor, 154 as this pattern was not available from the mass spectrum of 153. The percent intensities observed for the product of the crossover product match on the average within 3.4% of the calculated values for an intermolecular reaction. Therefore, the substitution reaction of 147 is not a case of endocyclic substitution.

Table 7: m/e(intensity) of a Fragment of 153 and of 154.

<table>
<thead>
<tr>
<th></th>
<th>d3</th>
<th>d2</th>
<th>d1</th>
<th>d0</th>
</tr>
</thead>
<tbody>
<tr>
<td>[OH][CHDNCH$_3$] $^*$</td>
<td>-</td>
<td>-</td>
<td>137(81)</td>
<td>136(19)</td>
</tr>
<tr>
<td>[CHO][OSO$_2$C$_2$H$_7$]</td>
<td>279(69)</td>
<td>278(22)</td>
<td>277(9.3)</td>
<td>-</td>
</tr>
</tbody>
</table>

With this lack of success in finding an example of endocyclic substitution involving a six-membered ring, the research was returned to finding an example which would
involve a five-membered ring.

N-Methyl-benzene-4-toluene-disulfonimide (160) was prepared using Baumgarten's procedure for the synthesis of disulfonimides. Generation of the sodium salt of sulfonamide 161 with sodium hydride followed by treatment with benzenesulfonyl chloride gave 160 (eq. 42).

\[
\begin{align*}
\text{CH}_3 & \text{ToISO}_2\text{NH} \xrightarrow{1.\text{NaH/DMF}} \text{CH}_3 \text{ToISO}_2\text{NISO}_2\text{Ph} \\
161 & \quad 160
\end{align*}
\] (42)

It was expected that n-butyllithium would deprotonate 160 at a position ortho to one of the sulfonyl groups. It was hoped that the carbanion 162 (or its isomer with lithium on the benzene ring) would attack sulfur to form a five-membered sulfurane, for example 163 (eq. 43). Sulfurane 163 could
pseudorotate so that the nitrogen could leave from an apical position to form 164. The other possible product 165 would result from an anion formed on the ortho position on the benzene ring. When disulfonimide 160 was treated with two equivalents of n-butyllithium in THF at -78°C, starting material was recovered in 23% yield and sulfonamide 161 was isolated in 2% yield (eq. 44). Attempts to isolate products from the many other bands in the chromatogram were unsuccessful. When the reaction was performed with three equivalents of n-butyllithium at room temperature, only 6% recovered starting material was obtained together with 28% yield of sulfonamide 161.

\[
\begin{align*}
\text{CH}_3 \quad \text{TolSO}_2N\text{SO}_2\text{Ph} & \xrightarrow{n-\text{BuLi}} \quad \text{CH}_3 \quad \text{TolSO}_2\text{NH} \quad + \quad 160 \\
& \quad 160 \quad 161
\end{align*}
\]

(44)

To understand this reaction further, a simpler disulfonamide was investigated. The bis-benzenedisulfonimide 166 was synthesized by Baumgarten's procedure\textsuperscript{51} from sulfonamide 167 (eq. 45). The synthesis of the required sulfonamide 167, by coupling methylamine with benzenesulfonyl chloride was complicated by the formation of mixtures of both 167 and
disulfonimide 166. The reaction of 166 with two
equivalents of n-butyllithium in THF at room temperature
led to 45% recovered starting material, 30% sulfonamide
167 and 22% of phenyl n-butyl sulfone (168) (eq. 46). When the reaction was performed with three equivalents
of n-butyllithium, starting material was recovered in
1.5% yield along with 43% of sulfonamide 167 and 29% of
sulfone 168. None of the rearranged product 169 was
isolated. The mechanism of the reaction of 166 with
n-butyllithium apparently involves nucleophilic attack
of n-butyllithium on the sulfonyl sulfur to create the
cleavage products 167 and 168. The formation of
sulfonamide 161 from the reaction of disulfonamide
160 with n-butyllithium, could arise from
nucleophilic attack on sulfur by n-butyllithium.
Alternatively, deprotonation of the N-methyl group,
elimination of benzenesulfinate anion, followed by hydride
attack at the imine carbon would result in sulfonamide
161.

\[
\begin{align*}
\text{CH}_3 & \quad \text{1. NaH/DMF} & \quad \text{CH}_3 \\
\text{PhSO}_2\text{NH} & \quad \text{DMF} & \quad \text{PhSO}_2\text{NSO}_2\text{Ph} \\
167 & \quad & 166 \\
\text{2. PhSO}_2\text{Cl} & \quad & \\
166 & \quad & \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{n-BuLi} & \quad \text{CH}_3 \\
\text{PhSO}_2\text{NSO}_2\text{Ph} & \quad \longrightarrow & \quad \text{PhSO}_2\text{NH} \\
166 & \quad & 167 & \quad & \text{PhSO}_2\text{nBu} \\
166 & \quad & 167 & \quad & 168 \\
\end{align*}
\]
Our attention next turned to Closson's rearrangement of $N$-methyl-$N$-phenyl-arenesulfonamides induced by alkylolithium bases. His examples of endocyclic substitution at sulfur(VI) involve four-membered cyclic structures of general formula 169; it is not known whether 169 is a transition state or an intermediate (eq. 48). Closson did a crossover experiment with a mixture of $N$-methyl-$N$-phenyl-4-toluenesulfonamide and $N$-methyl-$N$-(4'-methoxy)phenyl-4-methoxybenzene-sulfonamide and observed no crossover products. It was concluded that this reaction was intramolecular and, therefore, a case of endocyclic substitution. This crossover experiment was based on the assumption that there is a negligible rate difference between the rearrangement of
the two sulfonamides. To test this assumption and to make sure that this reaction was intramolecular, another crossover experiment was designed utilizing a mixture of deuterated and nondeuterated sulfonamides, since there would be little or no rate difference between the two. The reaction of \(N\)-methyl-\(N\)-phenyl-4-toluenesulfonamide (170) was reported by Closson to rearrange to (2-methylamino)phenyl 4-tolyl sulfone (171) in 52% yield (eq. 49).

\[
\begin{align*}
30 & \rightarrow 169 & \rightarrow 31 \\
\end{align*}
\]

The synthesis of sulfonamide 170 involved coupling 4-toluenesulfonyl chloride with aniline followed by \(N\)-methylation with potassium hydroxide and iodomethane. The rearrangement using \(n\)-butyllithium and Closson's conditions (THF, room temperature) resulted in 30% sulfone
The deuterated analog \textbf{172} was synthesized by the same methods used for the preparation of \textbf{170}, utilizing \textit{d}_3\text{-toluenesulfonyl chloride (119)} and \textit{d}_3\text{-iodomethane (Aldrich)}.

If the rearrangement was intramolecular, then only products \textbf{173} and \textbf{174} should be obtained (eq. 50).

The expected deuterium ratio of \(d_0 : d_3 : d_6\) would be 1 : 0 : 1. If the reaction was intermolecular, then the four sulfones \textbf{173} to \textbf{176} would be obtained.

In this case the \(d_0 : d_3 : d_6\) ratio would be 1 : 2 : 1. As the mass spectrum of \textbf{172} reveals proton isotopomers, the deuterium pattern of the \textit{d}_3\text{-methyl groups had to be taken into account. The expected percent intensities for intramolecular and intermolecular reactions were calculated in the same way as for the crossover reaction between \textbf{147} and \textbf{153}. The intermolecular calculations were based on the fragments from the mass spectrum of \textbf{172} (Table 8).

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
 & \text{m/e (intensity)} & \text{d3} & \text{d2} & \text{d1} \\
\hline
\textbf{(CD}_3\text{NHC}_6\text{H}_4\text{)}^+ & 109 (81) & 108 (5) & 107 (7) & 106(7) \\
\textbf{(CD}_2\text{C}_6\text{H}_4\text{SO}_2\text{)}^+ & 158 (48) & 157 (21) & 156 (16) & 155(15) \\
\hline
\end{tabular}
\caption{Fragments in the Mass Spectrum of \textbf{172}.}
\end{table}
Equimolar amounts of 170 and 172 were treated with two equivalents of \textit{n}-butyllithium, and the resulting rearranged product was isolated and analyzed by mass spectrometry. The percent deuterium in the product is in accord with a completely intramolecular reaction (Table 9). The percent intensities for \textit{d}_6 to \textit{d}_0 peaks observed for the product 177 match, on the average those calculated for an intramolecular reaction within 2.3\%. Therefore, it is concluded that the rearrangement of 170 is an example of endocyclic substitution at sulfur(VI). This result also supports the assumption made by Closson that the sulfonamides used in his crossover reaction react with very similar rates.
Table 9: Analysis of the Mass Spectrum of the Product of the Crossover Reaction of 170 and 172.

<table>
<thead>
<tr>
<th>m/e</th>
<th>267</th>
<th>266</th>
<th>265</th>
<th>264</th>
<th>263</th>
<th>262</th>
<th>261</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>d6</td>
<td>d5</td>
<td>d4</td>
<td>d3</td>
<td>d2</td>
<td>d3</td>
<td>d0</td>
</tr>
<tr>
<td>obs. % intensity of 170</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>14</td>
<td>81</td>
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<tr>
<td>obs. % intensity of 172</td>
<td>65</td>
<td>20</td>
<td>8</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>obs. % intensity of 177</td>
<td>33</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>calcd. % intensity (intramolecular)</td>
<td>32</td>
<td>10</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>41</td>
</tr>
<tr>
<td>calcd. % intensity (intermolecular)</td>
<td>10</td>
<td>5</td>
<td>4</td>
<td>37</td>
<td>7</td>
<td>6</td>
<td>31</td>
</tr>
</tbody>
</table>
CONCLUSIONS

In summary, endocyclic substitution at sulfur(VI) occurs when a four-membered cyclic intermediate or transition state is involved. Examples from the literature are Closson's \textsuperscript{35b} N-aryl arenesulfonamides \textbf{30} and Hellwinkel's \textsuperscript{37,41} extension of this reaction with sulfonamides such as \textbf{46, 61} and \textbf{67}. Our investigation of the rearrangement of \textbf{170} with deuterated analog \textbf{172} confirms that this reaction is intramolecular. Inspection of molecular models suggest that the four-membered cyclic intermediate is strained; yet the reaction proceeds well and presumably with retention at sulfur(VI).

An example of endocyclic substitution at sulfur(VI) involving five-membered rings has yet to be found. 2-Aminophenyl arenesulfonates, such as \textbf{97, 100} and \textbf{103}, rearrange to the corresponding sulfonamides. It may be that this rearrangement is endocyclic. The crossover experiment of \textbf{111} with deuterated analog \textbf{122} proved beyond a doubt that this rearrangement is intramolecular. However, the rearrangement of \textbf{129} to the corresponding sulfonamide as well as the isolation of the azobenzene from
the rearrangement of 91 makes the rearrangement of 2-aminoaryl arenesulfonates suspect. Sulfonate 129 can only rearrange through an elimination-addition pathway involving a quinonimine-type species or by an intermolecular pathway. The azobenzene would arise from a quinonimine. One way to shed additional light on the mechanism is to create a chiral sulfur(VI). Rearrangement of such an optically active sulfonate and observation of the stereochemistry might rule out one of the pathways. If an endocyclic mechanism is involved, retention or inversion of configuration at sulfur should be observed, resulting from a 90° or a 120° approach of the nucleophile, respectively. Retention of configuration at sulfur(VI) would also result from the elimination-addition pathway, because the sulfinate, which is eliminated from the molecule, retains its configuration about sulfur(IV). Work is continuing on this problem.

Disulfonimides 160 and 166 were investigated as they could potentially involve five-membered cyclic sulfuranes in the substitution reaction. Only the cleavage of these molecules was observed, probably resulting from nucleophilic attack at sulfur by n-butyllithium.

A search was made to find an example of endocyclic substitution at sulfur(VI) involving six-membered cyclic sulfuranes. Sulfonamide 133 was investigated and was found to undergo elimination in preference to substitution.
Both sulfone 141 and lithium 4-toluenesulfinate were isolated from the reaction mixture. Base evidently deprotonated the methyl of the N-methyl group which then eliminated 4-toluenesulfinate anion. Hydride attack on the resulting imine was proposed to explain the formation of sulfone 141.

Rearrangement of sulfonate 147 was investigated as theoretically it could proceed through a six-membered cyclic sulfurane. A crossover experiment of 147 with its deuterated analog, 153, revealed that the reaction was intermolecular and thus not a case of endocyclic substitution.

The investigation of the geometry of nucleophilic substitution at sulfur(VI) using endocyclic systems is based on an extremely interesting idea. If an example of retention or inversion of configuration at sulfur(VI) could be found, an important piece of information would be gained in our knowledge of substitution at sulfur. It is encouraging that a similar study on phosphorus successfully illustrated that a 90° approach to phosphorus is possible.25
EXPERIMENTAL

**Instrumentation.** $^1$H NMR spectra were recorded on a Varian EM360A instrument. $^{11}$B, $^{13}$C and $^{19}$F NMR spectra were recorded on a JEOL FX90Q instrument. $^1$H and $^{13}$C NMR spectra were referenced to internal TMS. $^{19}$F NMR spectra were referenced to external trifluoroacetic anhydride. $^{11}$B NMR spectra were referenced to internal boron trifluoride. Infrared spectra were recorded on a Perkin-Elmer 283B instrument. Elemental analyses and mass spectra were performed at the University of New Hampshire Instrumentation Center using a Perkin-Elmer 240B Elemental Analyzer and a Hitachi-Perkin-Elmer RMU-6E Mass Spectrometer.

**Materials.** Thin layer chromatography was performed on commercial pre-coated sheets (silica gel 60F-254 on aluminum, Sargent-Welch). All chemicals were reagent grade. Methylene chloride was distilled from phosphorus pentoxide. Ethyl acetate was distilled from calcium hydrde. Triethylamine was distilled from potassium hydroxide. Dimethylformamide was treated with barium oxide for 24 hours and then distilled under reduced pressure. Methanol was refluxed over magnesium turnings and iodine and then
distilled to prepare absolute methanol. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were first distilled from calcium hydride and then from sodium and benzophenone. 2-Aminophenol was recrystallized from ethyl acetate. 4-Toluenesulfonyl chloride was recrystallized from hexane. Aniline was distilled from zinc dust and sodium borohydride. Benzenesulfonyl chloride was treated with three mole percent each toluene and aluminum trichloride for 24 hours, then fractionally distilled (10 mm). All solids were weighed on an analytical balance to four significant figures; the weights were rounded off to three significant figures.

3-Trifluoromethybenzenesulfonyl Chloride
(98).53 Oleum (29 g, 62%) was added slowly through a pressure-equalizing addition funnel to trifluoromethylbenzene (30.0 g, 0.205 mol) in a round-bottomed flask equipped with a magnetic stirrer at 0°C. The addition was complete after two hours. The solution was stirred for twenty-four hours at room temperature. Saturated sodium chloride solution (100 mL) was added to quench the reaction. The white salt was filtered and dried thoroughly in a vacuum dessicator over P2O5 powder. The white salt was placed in a round-bottomed flask equipped with a magnetic stirrer. Phosphorus pentachloride (284 g, 1.36 mol) was added slowly via a powder funnel, which was then replaced by a reflux condenser. The slurry was heated until reflux in an oil
bath for fifteen hours. Toluene was added and then removed by vacuum distillation. The remaining liquid was transferred to a small distillation apparatus and the product fractionally distilled under vacuum to give 62.2% of 98 (31.1 g, 0.123 mol): bp 74°C (2.4 mm) (lit.\textsuperscript{53} 88-90°C, 5mm); IR (neat, NaCl plates) 3080, 1620, 1445, 1390, 1335 and 1140 (SO\textsubscript{2}Cl), 1290, 1190 (CF), 1110, 1070, 810 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 7.66 - 8.33 (m, 4 H); mass spectrum, m/e (intensity) 246 (20, M+2), 244 (60, M), 209 (335), 145 (1000). Anal. Calcd for C\textsubscript{7}H\textsubscript{4}ClF\textsubscript{3}O\textsubscript{2}S: C, 34.43; H, 1.65. Found: C, 34.51; H, 1.66.

2'-Aminophenyl 3-Trifluoromethylbenzenesulfonate (97). 2-Aminophenol (6.11 g, 0.0561 mol) was suspended in methylene chloride (50 mL) under nitrogen, in a flame-dried, round-bottomed flask equipped with a magnetic stirrer and a septum cap. The mixture was brought to 0°C with an ice bath. Triethylamine (5.92 g, 0.0585 mol) was added \textit{via} syringe and the mixture was stirred for five minutes. The septum cap was temporarily removed and under a fast flow of nitrogen, 3-trifluoromethylbenzenesulfonyl chloride (14.3 g, 0.0587 mol) was added through a powder funnel. The ice bath was removed and the solution was stirred at room temperature for one hour. The mixture was washed twice with water (20 mL), dried over anhydrous sodium sulfate, and filtered. The
solvent was removed and the product recrystallized from chloroform-petroleum ether to give 54.6% of 97 (9.71 g, 0.0306 mol): mp 106-107°C; IR (KBr) 3495 and 3405 (NH₂), 3080, 1640, 1610, 1500, 1370 and 1195 (SO₂O), 1330 (CF), 1125, 800, 760 cm⁻¹; ¹H NMR (CDCl₃) δ 3.7 (br s, 2H), 6.4-8.13 (m, 8H); ¹³C NMR (CDCl₃) δ 139.62, 135.89, 132.73, 131.75, 130.96 (J CF=4.4 Hz), 129.99, 128.31, 125.67 (J CF=4.4 Hz), 122.97 (J CF=272 Hz), 122.71, 118.42, 117.38; ¹⁹F NMR (CDCl₃) δ 14.62; mass spectrum, m/e (intensity) 317 (27, M), 209 (129), 145 (112), 108 (1000).
Anal. Calcd for C₁₃H₁₀F₃NO₃S: C, 49.21; H, 3.18; N, 4.41. Found: C, 49.14; H, 3.00; N, 4.45.

N-(2'-Hydroxyphenyl)-3-trifluoromethylbenzenesulfonamide (99). 2-Aminophenol (0.994 g, 9.11 mmol) was suspended under nitrogen in dry methylene chloride (20 mL) in a 50-mL round-bottomed flask equipped with a magnetic stirrer and a septum cap. The system was cooled to -78°C using a Dry Ice-acetone bath. Pyridine (0.452 mL, 5.01 mmol) and then a solution of 3-trifluoromethylbenzenesulfonyl chloride (1.11 g, 4.55 mmol) in methylene chloride (5 mL), were added successively via syringe. After the reaction had been stirred at -78°C for ten minutes, the Dry Ice-acetone bath was taken away and the solution was allowed to warm up to room
temperature. The reaction was monitored by TLC (methylen chloride) for the disappearance of the sulfonyl chloride. After five hours the reaction was complete. The solution was washed twice with water (10 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude orange solid was passed through a column of silica gel (ethyl acetate). The product was recrystallized from carbon tetrachloride to give 82.3% of 99 (1.19 g, 3.75 mmol): mp 125-126°C; IR (KBr) 3460 (OH), 3260 (NH), 3080, 1600, 1510, 1475, 1410, 1330 and 1170 (SO₂N), 1130 (CF), 1090, 1070, 310, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 1.63 (s, 1H), 5.90 (s, 1H), 6.6-7.9 (m, 8H); ¹³C NMR (d₆-acetone) δ 150.79, 142.40, 132.13, 131.74, 131.39 (²J CF=32.97 Hz), 130.96, 130.06 (³J CF=3.66 Hz), 127.77, 125.69, 124.86 (³J CF=4.15 Hz), 124.48 (¹J CF=272 Hz), 120.68, 116.42; ¹⁹F NMR (d₆-acetone) δ 17.96. Anal. Calcd for C₁₃H₁₀F₃NO₃S: C, 49.21; H, 3.18; N, 4.41. Found: C, 49.59; H, 3.11; N, 4.47.

Reaction of 2'-Aminophenyl 3-Trifluoromethylbenzenesulfonate (97) with n-Butyllithium.

2'-Aminophenyl-3-trifluoromethylbenzenesulfonate (0.110 g, 0.347 mmol) was dissolved in dry THF (60 mL) under nitrogen in a flame-dried, round-bottomed flask equipped with a magnetic stirrer and septum cap. The solution was brought to 0°C with an ice bath. n-Butyllithium (4
equivalents, 0.84 mL of a 1.6 M solution in hexane, 1.4 mmol) was introduced to the flask via dry syringe. The solution was stirred for one-half hour at 0°C followed by two hours at room temperature and then hydrolyzed with 10 mL of 5% aqueous hydrochloric acid solution. The THF was removed under reduced pressure and the remaining water was extracted three times with methylene chloride (60 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to give a black tar. Twelve spots were present on the TLC (20% petroleum ether, 80% methylene chloride); no starting material could be detected. No further work was attempted.

Reaction of 97 with Lithium Diisopropylamide.

2'-Aminophenyl 3-trifluoromethylbenzenesulfonate (0.50 g, 1.6 mmol) was placed under nitrogen in a flame-dried, round-bottomed flask equipped with a magnetic stirrer and a septum cap. Dry THF (60 mL) was added via syringe and the solution was brought to -78°C with a Dry Ice-acetone bath. Lithium diisopropylamide (LDA) (3 equivalents) was prepared under nitrogen in dry THF (5 mL) from diisopropylamine (0.65 mL, 4.6 mmol) and n-butyllithium (3.0 mL of a 1.6 M solution in hexane) in a flame-dried, round-bottomed flask equipped with a magnetic stirrer and a septum cap, and brought to -78°C. The solution of LDA was cannulated via a double-tipped needle into the
reaction flask and the solution was stirred for one-half hour. The Dry Ice-acetone bath was replaced by an ice bath, and the solution was stirred for four hours at 0°C. Water (20 mL) was added to quench the reaction. The THF was removed under reduced pressure and the remaining water was extracted twice with methylene chloride (80 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to give a crude orange solid. Recrystallization from carbon tetrachloride and petroleum ether yielded the sulfonamide 99 in 24.4% yield (0.124 g, 0.391 mmol): mp 124-125.5°C; IR (KBr) 3460 (OH), 3260 (NH), 1330 and 1170 (SO₂N), 1130 (CF) cm⁻¹; ¹H NMR (CDCl₃) δ 1.63 (s, 1H), 5.90 (s, 1H), 6.6-7.9 (m, 8H); mass spectrum, 317 (M).

3'- (2'-Amino)pyridyl 3-Trifluoromethylbenzene-sulfonate (100). The procedure was the same as for the synthesis of 99 except that 2-amino-3-hydroxypyridine (1.01 g, 9.16 mmol) was coupled to 3-trifluoromethylbenzenesulfonyl chloride (2.39 g, 9.82 mmol). The crude product was purified by recrystallization from carbon tetrachloride to give 66.7% of 100 (1.95 g, 6.11 mmol): mp 111-113.5°C; IR (KBr) 3500 and 3330 (NH₂), 3120, 3040, 2950, 1655, 1620, 1500, 1390 and 1160 (SO₂O), 1340, 1210, 1140, 1075, 810, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 4.70 (br s, 2H), 6.43-8.13 (m, 8H);
$^{13}$C NMR (CDCl$_3$): 152.17, 146.90, 136.50, 132.99, 131.69, 131.62 ($^3$J$_{CF}$=5.86 Hz), 130.32, 129.09, 125.64 ($^3$J$_{CF}$=3.91 Hz), 122.91 ($^1$J$_{CF}$=272 Hz), 113.93; $^{19}$F NMR (CDCl$_3$): 11.71. Anal. Calcd for C$_{12}$H$_9$F$_3$N$_2$O$_2$S: C, 45.28; H, 2.85; N, 8.80. Found: C, 45.08; H, 2.91; N, 8.66.

**Attempted Synthesis of N-2'-[(3'-Hydroxy)-pyridyl]-3-trifluoromethylbenzenesulfonamide (101).**

**Method 1:** 2-Amino-3-hydroxypyridine (1.5 equivalents, 0.392 g, 3.56 mmol) was coupled to 3-trifluoromethylbenzenesulfonyl chloride (0.579 g, 2.37 mmol) according to the procedure for the synthesis of 99 except that it was done at room temperature. The crude product was purified by column chromatography (silica gel, ethyl acetate) to yield 75.6% 3'- (2'-amino)pyridyl 3-trifluoromethylbenzenesulfonate (100) (0.571 g, 1.79 mmol): mp 109-111°C; IR (KBr) 3500 and 3330 (NH$_2$), 3120, 1390 and 1160 (SO$_2$O) cm$^{-1}$; $^1$H NMR (CDCl$_3$): 4.70 (br s, 2H), 6.43-8.3 (m, 8H).

**Method 2:** 2-Amino-3-hydroxypyridine (1.5 equivalents, 0.418 g, 3.80 mmol) was coupled to 3-trifluoromethylbenzenesulfonyl chloride (0.618 g, 2.53 mmol) at -78°C according to the procedure for the synthesis of 99. The crude product was purified by column chromatography (silica gel, 1 methylene chloride: 0.1 ethyl acetate) to yield 74.2% 3'- (2'-amino)pyridyl
3-trifluoromethylbenzenesulfonate (100) (0.598 g, 1.88 mmol): mp 110-113°C; IR (KBr) 3500 and 3330 (NH), 3120, 1330 and 1160 (SO2) cm⁻¹; ¹H NMR (CDCl₃) δ 4.70 (br s, 2H), 6.43-8.13 (m, 8H).

Reaction of 3'-((2'-Amino)pyridyl 3-Trifluoromethylbenzenesulfonate (100) with Lithium Diisopropylamide.

3'-((2'-Amino)pyridyl 3-trifluoromethylbenzenesulfonate (0.25 g, 0.78 mmol) was dissolved in dry THF (40 mL) under nitrogen in an over-dried, round-bottomed flask equipped with a magnetic stirrer and septum cap. Lithium diisopropylamide (LDA) (3 equivalents) was prepared under nitrogen in dry THF (5 mL) from diisopropylamine (0.33 mL, 2.3 mmol) and n-butyllithium (1.5 mL of a 1.6 M solution in hexane, 1.2 mmol) in an oven-dried, round-bottomed flask equipped with a magnetic stirrer and septum cap. Both solutions were brought to -78°C with Dry Ice-acetone baths. The solution of LDA was cannulated into the solution of sulfonate ester via a double-tipped needle. The reaction was monitored by TLC (methylene chloride) and after one hour the solution was allowed to warm to 0°C by switching to an ice bath. After two hours at 0°C, the reaction was quenched with 10 mL of 5% aqueous hydrochloric acid solution. The solvent was removed under reduced pressure, water (10 mL) was added and the product was extracted three times with methylene chloride (90 mL). The combined organic layers were dried over anhydrous magnesium
sulfate, filtered, and the solvent removed under reduced pressure. The crude solid was recrystallized from carbon tetrachloride to yield recovered starting material in 12.5% yield (0.0311 g, 0.098 mmol): mp 109-112°C; IR (KBr) 3500 and 3330 (NH\textsubscript{2}), 3120, 1390 and 1160 (SO\textsubscript{2}O) cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textsuperscript{8} 4.70 (br s, 2H), 6.43-8.13 (m, 8H). The aqueous layer from the above extraction was acidified with 10% aqueous hydrochloric acid solution and reextracted three times with methylene chloride (90 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude solid was recrystallized from carbon tetrachloride to yield 52% N-2'-[(3'-hydroxy)-pyridyl]-3-trifluoromethylbenzenesulfonamide (101) (0.13 g, 0.41 mmol): mp 136-138°C; IR (KBr) 3485 (OH), 3300 (NH\textsubscript{2}), 3120, 2920, 1650, 1600, 1490, 1390, 1330 and 1150 (SO\textsubscript{2}N), 1200, 800, 740, 590, 550 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textsuperscript{8} 6.50-8.13 (m, 9H); \textsuperscript{19}F NMR (CDCl\textsubscript{3}) \textsuperscript{8} 13.27. Anal. Calcd for C\textsubscript{12}H\textsubscript{9}F\textsubscript{3}N\textsubscript{2}O\textsubscript{3}S: C, 45.16; H, 2.70; N, 8.56. Found: C, 45.19; H, 2.71; N, 8.58.

2-Trifluoromethylbenzenesulfonyl Chloride (102).

2-Trifluoromethylaniline (43.4 g, 0.269 mol) was suspended in concentrated hydrochloric acid (425 mL) in an oven-dried, round-bottomed flask equipped with a magnetic stirrer, a condenser and an addition funnel reaching close to the bottom of the diazotizing vessel.\textsuperscript{55} The solution was
heated until the hydrochloride salt dissolved; then the solution was cooled to 10°C. A solution of sodium nitrite (23 g) in water (80 mL) was added dropwise. The turbid orange solution of the diazonium chloride was filtered, and excess nitrous acid was destroyed with sulfamic acid until no more blue color was seen on starch-iodide paper. The solution was poured into a green solution of glacial acetic acid (1L) saturated with SO₂ to which a solution of CuCl₂ (8 g) dissolved in water (65 mL) had been added. As nitrogen evolved, the solution turned black and then light green. A yellow oil separated to the bottom of the beaker. The oil was separated in a separatory funnel, dissolved in ether, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure and the crude oil was fractionally distilled to give 53.5% of 102 (35.2 g, 0.144 mol): bp 90-95°C (1.8mm), (lit. 53 bp 125°C, 5mm); mp 23-24°C; IR (neat, NaCl plates) 3095, 3075, 3020, 1590, 1430, 1380 (CF), 1305 and 1180 (SO₂Cl), 1270, 1140, 1090, 1030, 760, 700, 530 cm⁻¹; ¹H NMR (CDCl₃) ∑ 7.43-8.66 (m, 4H); ¹³C NMR (CDCl₃) ∑ 141.92, 135.73, 133.34, 131.30, 128.88 (²Jₙ=6.18 Hz), 127.40 (²Jₙ=35.15 Hz), 122.05 (¹Jₙ=275 Hz); ¹⁹F NMR (CDCl₃) ∑ 18.89.

3'-(2'-Amino)pyridyl 2-Trifluoromethylbenzene-sulfonate (103). 2-Amino-3-hydroxypyridine (1.0 g, 9.1
mmol) was coupled with 2-trifluoromethylbenzenesulfonyl chloride (2.57 g, 9.88 mmol) according to the method used for the synthesis of 97. The crude product was recrystallized from ethanol five times to give a 35.5% yield of 103 (1.03 g, 3.23 mmol): mp 114-115°C; IR (KBr) 3490 and 3280 (NH$_2$), 3130, 1640, 1490, 1380 and 1145 (SO$_2$O), 1310 (CF), 1270, 1190, 1090, 810, 760, 590, 570, 550 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 4.66 (br s, 2H), 6.46-8.2 (m, 7H); $^{13}$C NMR (CDCl$_3$) $\delta$ 152.18, 146.70, 134.81, 133.84, 132.89, 128.90, 131.86, 130.48, 128.90 ($^3$J$_{CF}$=6.1 Hz), 127.73 ($^2$J$_{CF}$=31.13 Hz), 122.27 ($^1$J$_{CF}$=272 Hz), 113.93. Anal. Calcd for C$_{12}$H$_9$F$_3$N$_2$O$_3$S: C, 45.30; H, 2.85; N, 8.80. Found: C, 45.70; H, 2.80; N, 8.64.

**Attempted Synthesis of N-2'-[(3'-Hydroxy)-pyridyl]-2-trifluoromethylbenzenesulfonamide (104).**

2-Amino-3-hydroxy pyridine (1.1 equivalents, 1.85 g, 0.0168 mol) was coupled to 2-trifluoromethylbenzenesulfonyl chloride (3.73 g, 0.0153 mol) according to the procedure for the synthesis of 99. The crude product was purified by column chromatography (silica gel, 1:1 methylene chloride, ethyl acetate) and then again by column chromatography (silica gel, methylene chloride) to give 48.4% yield of 3'-(2'-amino)pyridyl 2-trifluoromethylbenzenesulfonate (103) (2.35 g, 7.41 mmol): mp 113-115°C; IR (KBr) 3490 and 3280 (NH$_2$), 3130, 1380 and 1145 (SO$_2$O),
1310 (CF) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.66 (br s, 2H), 6.46-8.2 (m, 7H).

**Reaction of 3'-(2'-Amino)pyridyl 2-Trifluoromethylbenzenesulfonate (103) with n-Butyllithium.**

3'-(2'-Amino)pyridyl 2-trifluoromethylbenzenesulfonate (0.080 g, 0.25 mmol) was dissolved in dry THF (50 mL) under nitrogen in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer and a septum cap. n-Butyllithium (3 equivalents, 0.47 mL of a 1.6 M solution in hexane, 1.4 mmol) was introduced to the flask via dry syringe. The solution was monitored by TLC (ethyl acetate) which showed no more starting material after one hour. The reaction was quenched with 10 mL of a 10\% aqueous sulfuric acid solution. The THF was removed under reduced pressure and the remaining water was extracted three times with methylene chloride (60 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude yellow oil was purified by column chromatography (silica gel, ethyl acetate) and then again by column chromatography (silica gel, methylene chloride) to yield 51\% of N-2'-[3'-hydroxy)pyridyl]-2-trifluoromethylbenzenesulfonamide (104) (0.041 g, 0.13 mmol), as a viscous oil: IR (KBr) 3360 (OH), 3220 (NH), 3120, 2950, 2920, 1635, 1590, 1540, 1420, 1355, 1305 and 1130 (SO\(_2\)N), 1260, 1170, 1080, 1030, 960, 760 cm\(^{-1}\);
$^1$H NMR (CDCl$_3$) $\delta$ 6.45-8.42 (m, 9H); mass spectrum, m/e (intensity), 318 (87, M), 261 (119), 201 (75), 145 (95), 109 (401), 106 (316).

2'-Aminophenyl 4-Toluene sulfonate (114).

2-Aminophenol was sulfonated with 4-toluene sulfonyl chloride and triethylamine in dry methylene chloride under nitrogen according to the procedure of Linda Yildiz$^7$ except that it was done at $-78^\circ$C. The crude solid was recrystallized from ethanol to yield 80.6% 114: mp 99-101°C (lit. $65 - 100 - 101^\circ$C); IR (KBr) 3500 and 3400 (NH$_2$), 1615, 1490, 1360 and 1150 (SO$_2$O), 1310, 1185, 1170, 870, 790, 650, 540 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.43 (s, 3H), 3.80 (br s, 2H), 6.56-7.83 (m, 8H).

2'-Formamidophenyl 4-Toluene sulfonate (115).

Following Krishnamurthy's procedure,$^{47}$ the amine group of 114 (10.0 g, 0.0379 mol) was formylated with acetic formic anhydride prepared in situ from acetic anhydride (15.5 g, 0.152 mol) and formic acid (6.12 g, 0.133 mol). The crude product was recrystallized from ethanol to yield 79.9% 115 (8.84 g, 0.0303 mol): mp 130-132°C; IR (KBr) 3325 (NH), 3065, 2930, 1680 (C=O), 1540, 1460, 1380 and 1170 (SO$_2$O), 870, 780 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.46 (s, 3H), 6.86-7.86 (m, 8H), 8.23 and 8.33 (2 s, 2H). Anal. Calcd for C$_{14}$H$_{13}$NO$_4$S: C, 57.72; H, 4.50; N, 4.81. Found: C, 57.62; H, 4.52; N, 4.81.
Method 1: 47 Sulfonate ester 115 (0.636 g, 2.18 mmol) was dissolved in dry THF (25 mL) under nitrogen in an oven-dried, round-bottomed flask equipped with a magnetic stirrer, septum cap, and reflux condenser. Borane:tetrahydrofuran complex (2.5 equivalents, 5.46 mL, 2.18 mmol) was added via syringe. After gas evolution had ceased, the flask was fitted with a heating mantle and the solution was refluxed for one hour. The reaction was monitored by TLC (methylen chloride). The solution was allowed to cool to room temperature, methanol (10 mL) was added slowly and the solution was stirred for one-half hour. The solvent was removed under reduced pressure, methylene chloride (50 mL) was added and the solution was washed three times with water (60 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was recrystallized from ethanol to give 74.4% 111 (0.450 g, 1.62 mmol): mp 64-65°C (lit. 46 mp 66-67°C); IR (KBr) 3460 (NH), 3080, 3020, 1625, 1535, 1370 and 1200 (SO20), 1095, 875, 760, 565 cm⁻¹; ¹H NMR (CDCl₃) 2.26 (s, 3H), 2.56 (d, 3H), 3.96 (br s, 1H), 6.26-7.7 (m, 3H); ¹³C NMR (CDCl₃) 145.41, 142.16, 136.82, 132.73, 129.67, 128.44, 127.98, 122.13, 116.01, 111.66, 30.04, 21.65; mass spectrum, m/e (intensity) 278 (4, M+1), 277 (25, M), 155 (169), 122 (1000), 108 (121), 91
Method 2: \(^{73-75}\) Lithium aluminum hydride (0.283 g, 7.59 mmol) was placed in an oven-dried, round-bottomed flask equipped with a mechanical stirrer with a water-cooled jacket adapter, a pressure-equalizing addition funnel, a reflux condenser and a nitrogen inlet and outlet. Dry THF (15 mL) was added and the system was cooled to 0°C with an ice bath. A solution of 115 (0.538 g, 1.85 mmol) in THF (15 mL) was added slowly to the mixture. The reaction mixture was stirred for ten hours and it was monitored by TLC (chloroform). The reaction was quenched with water (5 mL), after two hours dilute aqueous sodium hydroxide solution (10 mL) was added and then after twenty minutes of stirring, more water (5 mL) was added. The mechanical stirrer was stopped. After ten minutes, the reaction mixture was filtered, and the solid was washed with ether. The solvent was removed under reduced pressure to yield an oil. The oil was dissolved in methylene chloride, washed with 10% aqueous hydrochloric acid solution (30 mL). The aqueous layer was extracted with methylene chloride (30 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (silica gel, methylene chloride) to yield 20.9% of 111 (0.107 g, 0.386 mmol): mp 64-65°C (lit. \(^{46}\) mp 66-67°C); IR (KBr) 3460 (NH), 1370 and
1200 (SO₂O) cm⁻¹; ¹H NMR (CDCl₃) δ 2.26 (s, 3H), 2.56 (d, 3H), 3.96 (br s, 1H), 6.26-7.7 (m, 8H); and 69.6% yield of N-methyl-N-(2'-hydroxyphenyl)-4-toluenesulfonamide (112) (0.357 g, 1.29 mmol): mp 122.5-124°C (lit. mp 125-126°C); IR (KBr) 3480 (OH), 3055, 3005, 2960, 2940, 1600, 1500, 1460, 1335 and 1150 (SO₂N), 1195, 1090, 810, 760 cm⁻¹; ¹H NMR
(CDCl₃) δ 2.43 (s, 3H), 3.16 (s, 3H), 6.35-7.63 (m, 9H); ¹³C NMR (CDCl₃) δ 153.79, 144.37, 132.27, 129.67, 129.51, 128.44, 128.34, 126.06, 120.37, 117.64, 39.34, 21.59; mass spectrum, m/e (intensity) 278 (15, M+1), 277 (71, M), 123 (95), 122 (1000), 94 (202), 91 (80).

Reaction of 111 with Lithium Diisopropylamide at -78°C. Sulfonate ester (111) (0.316 g, 1.14 mmol) was dissolved in dry THF (30 mL) under nitrogen in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer, septum cap and a nitrogen inlet and outlet. Lithium diisopropylamide (3 equivalents) was prepared in dry THF (20 mL) under nitrogen from diisopropylamine (0.65 mL, 4.5 mmol) and n-butyllithium (2.1 mL of a 1.6 M solution in hexane, 3.4 mmol) in an oven-dried, round-bottomed flask equipped with a magnetic stirrer and septum cap. Both solutions were brought to -78°C with Dry Ice-acetone baths. The solution of LDA was cannulated into the solution of sulfonate ester via
a double-tipped needle. The reaction was monitored by TLC (methylene chloride). The solution was quenched after one hour with 10% aqueous hydrochloric acid solution (5 mL). The solution was allowed to warm to room temperature and the THF was removed under reduced pressure. The remaining aqueous mixture was extracted three times with ethyl acetate (150 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography (silica gel, methylene chloride) to yield 80.5% recovered starting material (0.255 g, 0.919 mmol): mp 64-65°C; IR (KBr) 3460 (NH), 1370 and 1200 (SO2) cm⁻¹; ¹H NMR (CDCl₃) δ 2.26 (s, 3H), 2.56 (d, 3H), 3.96 (br s, 1H), 6.26-7.7 (m, 8H); and 4.55% yield of 112 (0.0144 g, 0.0519 mmol): mp 119-121°C; IR (KBr) 3480 (OH), 1335 and 1150 (SO2N) cm⁻¹; ¹H NMR (CDCl₃) δ 2.43 (s, 3H), 3.16 (s, 3H), 6.35-7.6 (m, 9H).

Reaction of 111 with Lithium Diisopropylamide at Room Temperature. The procedure was the same as for the reaction at -78°C except that 111 (0.296 g, 1.07 mmol) was dissolved in dry THF (30 mL) and treated with LDA (three equivalents) at room temperature. After one hour the reaction was quenched with 10% aqueous hydrochloric acid solution (2 mL) and the THF was removed under reduced pressure. The remaining aqueous mixture was extracted three times with ethyl acetate (60 mL). The combined organic
layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (silica gel, methylene chloride) to yield 43.8% rearranged product 112 (0.130 g, 0.468 mmol): mp 122-123°C (lit. mp 125-126°C); IR (KBr) 3480 (OH), 1335 and 1150 (SO₂N) cm⁻¹; ¹H NMR (CDCl₃) δ 2.43 (s, 3H), 3.16 (s, 3H), 6.35-7.63 (m, 9H).

4-d₇-Toluenesulfonyl Chloride (116).

d₈-Toluene (2.52 g, 0.0251 mol, Aldrich) was chlorosulfonated with chlorosulfonic acid (5.4 equivalents, 11 mL, 0.13 mol) in chloroform at -56°C under nitrogen according to the procedure of Clarke, Babcock and Murray. The reaction was quenched by pouring into crushed ice, and the product was extracted and recrystallized from hexane to yield 63% 116 (3.1 g, 0.016 mol): mp 66-67°C (lit. mp 67-68°C); IR (KBr) 3040, 1570 (CD), 1360 and 1170 (SO₂C₁), 1070, 750, 610, 545, 510 cm⁻¹; ¹³C NMR (CDCl₃) δ 146.77, 141.70, 130.26, 127.00, 21.39 (¹JC-D =19.54 Hz, septet); mass spectrum, m/e (intensity) 198 (24, M+1), 197 (60, M), 196 (93), 195 (107), 194 (78), 193 (21), 162 (72), 161 (210), 160 (336), 159 (242), 158 (72).

2'-(Formyl)phenyl 4-Toluenesulfonate. This sulfonate ester was prepared according to the procedure for the non-deuterated analog 148 except that
salicylaldehyde (2 equivalents, 0.54 mL, 5.1 mmol) was coupled to 4-d$_7$-toluenesulfonyl chloride (0.501 g, 2.53 mmol). Excess salicylaldehyde was removed at the end of the reaction by kugelrohr distillation. The crude product was recrystallized from cyclohexane to yield 61.7% of 2'-(formyl)phenyl 4-toluenesulfonate (0.443 g, 1.56 mmol): mp 61°C (lit. 61 mp 63-64°C); $^1$H NMR (CDCl$_3$) $\delta$ 7.12-7.95 (m, 6.75H), 10.03 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 187.29, 151.26, 146.25, 135.33, 131.36, 130.13, 129.35, 128.70, 128.50, 127.53, 123.75; mass spectrum, m/e (intensity) 284 (15, M+1), 283 (36, M), 282 (62), 281 (69), 280 (172), 279 (152), 162 (129), 161 (294), 160 (347), 159 (290), 158 (125).

(2'-Aminophenyl) 4-d$_7$-Toluenesulfonate (117). Sulfonate ester 117 was prepared according to the procedure of Yildiz$^7$ except that 2-aminophenol (2 equivalents, 0.504 g, 4.62 mmol) was coupled to 4-d$_7$-toluenesulfonyl chloride (0.457 g, 2.31 mmol) at -78°C. The crude product was recrystallized from ethanol twice to yield 17.7% 117 (0.221 g, 0.818 mmol): mp 100-101°C (lit. 65 mp 100-101°C); $^1$H NMR (CDCl$_3$) $\delta$ 3.76 (br s, 2H), 6.53-7.83 (m, 8H); $^{13}$C NMR (CDCl$_3$) $\delta$ 139.75, 137.02, 129.80, 128.44, 127.79, 122.91, 118.29, 117.18; mass spectrum, m/e (intensity) 271 (6, M+1), 270 (22, M), 269 (122), 268 (171), 267 (167), 266 (15), 108 (1000).
\( \alpha, \alpha, \alpha-d_3 \)-Toluene (118). Benzotrichloride (67.2 mL, 0.474 mol) was reduced with zinc and acetic acid-\( d_1 \) (145 g, 2.37 mol, prepared by hydrolysis of acetyl chloride [freshly distilled from dimethylaniline] with deuterium oxide) to 118 in 12\% yield (5.3 g, 0.056 mol) by the method of Renaud and Leitch:49 bp 110°C (lit.49 110°C); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 2.3 (br s, 0.37H), 7.2 (s, 5H); mass spectrum, m/e (intensity), 96 (76, M+1), 95 (1000, M), 94 (846), 93 (656), 92 (214), 91 (76).

\( 4-d_3 \)-Methylbenzenesulfonyl Chloride (119). \( \alpha, \alpha, \alpha-d_3 \)-Toluene (2.83 g, 0.0298 mol) was chlorosulfonated with chlorosulfonic acid (8 equivalents, 20 mL, 0.24 mol) in chloroform (25 mL) under nitrogen at 0°C according to the method of Clarke, Babcock and Murray.63 The reaction was quenched by pouring into crushed ice. The crude product was recrystallized from hexane to yield 26.0\% 119 (1.50 g, 7.75 mmol): mp 65.5-67°C (lit.64 mp 67-68°C); IR (KBr) 3080, 3040, 1580 (CD), 1370 and 1170 (SO\(_2\)Cl), 1070, 880, 770, 615, 550, 510 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 2.43 (br s, 0.4H), 7.33-8.01 (m, 4H); \(^13\)C NMR (CDCl\(_3\)) \( \delta \) 146.61, 141.83, 130.22, 127.07; mass spectrum, m/e (intensity) 195 (55, M+2), 194 (32, M+1), 193 (157, M), 192 (171), 191 (20), 160 (21), 159 (172), 158 (394), 157 (121), 156 (56), 155 (13), 94 (1000), 93 (323), 92 (176), 91 (67).

\( (2'-d_2\)-Methylamino)phenyl 4-Toluenesulfonate
Sulfonate ester (123) was prepared according to the procedure for the synthesis of the nondeuterated analog 111 except that BD$_3$:THF complex was used, $^{11}$B NMR showed the reagent was 0.43 M concentration). The sulfonate ester 115 (0.0842 g, 0.289 mmol) was reduced at room temperature and the crude product was recrystallized from ethanol to yield 62% 123 (0.050 g, 0.18 mmol): mp 62°C (lit. mp 66-67°C); IR (KBr) 3430 (NH), 3040, 3020, 2960, 2900, 1610, 1510, 1355 and 1190 (SO$_2$O), 1150, 1075, 865, 740, 555 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.35 (s, 3H), 2.60 (s, 1H), 3.90 (br s, 1H), 6.5-7.8 (m, 8H); mass spectrum, m/e (intensity) 280 (19, M+1), 279 (100, M), 278 (112), 277 (166), 124 (783), 123 (1000), 122 (315).

2'-Aminophenyl 4-d$_3$-Methylbenzenesulfonate (120). Sulfonate ester 120 was prepared according to the procedure 7 for the nondeuterated analog 114 except that 2-aminophenol (2 equivalents) was coupled with 4-d$_3$-methylbenzenesulfonyl chloride (0.0671 g, 0.348 mmol) at -78°C. The crude product was purified by column chromatography (silica gel, methylene chloride) and then recrystallized from ethanol to yield 92.3% of 120 (0.0854 g, 0.321 mmol): mp 100-101°C (lit. mp 100-101°C); IR (KBr) 3500 and 3410 (NH$_2$), 3080, 2940, 2880, 1950 (CD), 1620, 1490, 1360 and 1150 (SO$_2$O), 1315, 1185, 1170, 870, 790, 650, 540 cm$^{-1}$; $^1$H NMR
(CDCl$_3$) $\delta$ 2.40 (br s, 0.66H), 3.77 (br s, 2H), 6.53-7.82 (m, 8H); $^{13}$C NMR (CDCl$_3$) $\delta$ 145.41, 142.49, 137.09, 132.86, 129.80, 128.57, 127.79, 122.98, 118.29, 117.19; mass spectrum, m/e (intensity) 267 (5, M+1), 266 (34, M), 265 (8), 158 (5), 108 (1000), 94 (94), 93 (166), 92 (19), 91 (12).

(2'-d$_3$-Methylamino)phenyl 4-d$_3$-Methylbenzenesulfonate (122). 2'-d$_1$-Formamidophenyl 4-d$_3$-methylbenzenesulfonate (121) was prepared first according to the procedure for the nondeuterated analog 115 except that 120 (0.0789 g, 0.2965 mmol) was formylated with acetic d$_1$-formic anhydride (prepared from acetic anhydride [freshly distilled from dimethylaniline] and d$_2$-formic acid [Chemical Dynamics Corp.]). The crude product was recrystallized from ethanol: $^1$H NMR (CDCl$_3$) $\delta$ 2.46 (br s, 0.29H), 6.86-7.86 (m, 8H), 8.23 and 8.33 (2 s, 1.1H). The crystals and residue from the mother liquor were combined and dissolved in dry THF and were reduced with BD$_3$:THF (2.5 equivalents, 0.741 mmol) according to the procedure for the nondeutered analog 111. The crude product was purified by column chromatography (silica gel, methylene chloride) to yield 42.8% 122 (0.0359 g, 0.127 mmol): mp 63-64°C (lit. $^4$6 mp 66-67°C); IR (KBr) 3460 (NH), 1950 (CD), 1620, 1520, 1365 and 1185 (SO$_2$O), 1160, 1090, 370, 750, 550 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.26 and 2.56 (2 s,
1.38H), 3.96 (br s, 1H), 6.26-7.7 (m, 8H); $^{13}$C NMR (CDCl$_3$) $\delta$ 145.34, 142.23, 136.83, 132.79, 129.67, 128.89, 127.98, 122.13, 116.02, 111.66, 29.66; mass spectrum, m/e (intensity) 284 (14, M+1), 283 (51, M), 282 (67), 281 (153), 280 (11), 158 (16), 125 (791), 124 (1000), 123 (35%), 122 (20), 94 (146), 93 (53), 92 (166), 91 (19).

Crossover reaction of 111 and 122 with Lithium Diisopropylamide. Equimolar amounts of sulfonate esters 111 (0.0212 g, 0.0765 mmol) and 122 (0.0226 g, 0.0798 mmol) were dissolved in dry THF (50 mL) in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer, a septum cap and a nitrogen inlet and outlet. Lithium diisopropylamide (3 equivalents, 0.48 mmol) was prepared in dry THF (20 mL) under nitrogen from diisopropylamine (0.090 mL, 0.64 mmol) and n-butyllithium (0.30 mL of a 1.6 M solution in hexane, 0.48 mmol) in an oven-dried, round-bottomed flask equipped with a magnetic stirrer and a septum cap. The solution of LDA was cannulated into the solution of sulfonate esters via a double-tipped needle. The reaction was monitored by TLC (methylene chloride). After one hour the reaction was quenched with 10% aqueous sulfuric acid solution. The solvent was removed and the remaining aqueous mixture was extracted three times with methylene chloride (60 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced
pressure. The crude material was purified by column chromatography (silica gel, methylene chloride) to yield 54.0% of the rearranged product (0.0236 g): mp 121-122°C (mp of 112: 125-126°C); IR (KBr) 3480 (OH), 3060, 3005, 2970, 2940, 1600, 1500, 1460, 1335 and 1145 (S=O), 1195, 1090, 815, 760 cm⁻¹; ¹H NMR (CDCl₃) δ 2.43 (s, 1.5H), 3.16 (s, 1.5H), 6.35-7.63 (m, 9H); ¹³C NMR (CDCl₃) δ 153.77, 144.34, 132.28, 129.64, 129.51, 128.34, 128.08, 126.03, 120.38, 117.64, 39.32, 21.59; mass spectrum, m/e (intensity) 284 (15), 283 (72), 282 (93), 281 (53), 280 (20), 279 (16), 278 (117), 277 (142).

Carbamidic Acid, N,N'-dicyclohexyl methyl ester (134).

Equimolar amounts of N,N'-dicyclohexyl carbodiimide (14.4 g, 0.125 mol) and absolute methanol (2.82 mL, 0.125 mol) were combined with a small amount of CuCl (0.014 g, 0.14 mmol), and the mixture was stirred for 72 hours at room temperature. The product was fractionally distilled to give 93.7% yield of 134 (15.5 g, 0.0652 mol): bp 110°C, 3mm; mp 32-33°C (lit. 50 mp 32-33°C); IR (neat, NaCl plates) 3435 (NH), 2930, 2860, 1655, 1330 cm⁻¹; ¹H NMR (CDCl₃) δ 1.25-1.65 (m, 22H), 2.75 (br s, 1H), 3.65 (s, 3H).
2-Aminothioanisole (135).

**Method 1:**
Equivalent amounts of 2-aminothiophenol (4.74 g, 0.0379 mol) and carbamidic acid, N,N'-dicyclohexylmethyl ester (134) (9.03 g, 0.0379 mol) were heated together in benzene (50 mL) at 80°C for two hours. The solution was allowed to cool to room temperature and the N,N'-dicyclohexylurea was suction filtered and washed with methylene chloride. The solvent was removed under reduced pressure and the crude oil purified by fractional distillation to yield 93.4% of 135 (4.92 g, 0.0354 mol): bp 64°C, 0.2mm (lit. 57 bp 133°C, 15mm); IR (neat, NaCl plates) 3460 and 3370 (NH), 3075, 3025, 3000, 2930, 1615, 1490, 1455, 1310, 750 cm⁻¹; \(^1\)H NMR (CDCl₃) δ 2.31 (s, 3H), 4.13 (br s, 2H), 6.6-7.5 (m, 4H).

**Method 2:**
2-Aminothiophenol (32.27 g, 0.253 mol) was dissolved in methanol (100 mL) and sodium (5 g), freshly cut into small pieces, was added gradually. Methyl iodide (9.65 mL, 0.155 mol) was added and the solution was refluxed for ninety minutes. The solution was cooled and then poured into water (500 mL). The oil was extracted into methylene chloride, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude brown oil was fractionally distilled to give 91.81% yield of
135 (19.784 g, 0.1423 mol): bp 65°C (0.2mm) (lit. bp 133°C, 15mm); IR (neat, NaCl plates) 3460 and 3370 (NH$_2$) cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.31 (s, 3H), 4.13 (br s, 2H), 6.6-7.5 (m, 4H).

N-[(2'-methylthio)phenyl]-4-toluenesulfonamide (136). 2-Aminothioanisole (11 g, 0.079 mol) was dissolved in ether (250 mL) at 0°C in a 500-mL round-bottomed flask equipped with a magnetic stirrer. Pyridine (6.4 mL, 0.079 mol) and then 4-toluenesulfonyl chloride (22.6 g, 0.118 mol) were added successively. The solution was allowed to warm to room temperature and was stirred for 18 hours. The pyridine-hydrochloride salt was filtered and washed with ether. The combined ether solutions were washed twice with water (50 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude solid was recrystallized from ethanol to give 32.7% yield of 136 (19.2 g, 0.0654 mol): mp 146-147°C; IR (KBr) 3260 (NH), 3030, 2920, 1385, 1320 and 1140 (SO$_2$N), 815, 750, 535 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.16 (s, 3H), 2.36 (s, 3H), 7.2-7.83 (m, 9H); $^{13}$C NMR (CDCl$_3$) $\delta$ 143.91, 141.12, 137.41, 136.24, 133.38, 129.54, 128.96, 127.27, 125.05, 120.31, 21.46, 19.05. Anal. Calcd for C$_{14}$H$_{15}$NO$_2$S$_2$: C, 57.33; H, 5.16; N, 4.78. Found: C, 57.67; H, 5.12; N, 4.87.

N-Methyl-N-[(2'-Methylthio)phenyl]-
4-Toluenesulfonamide (137).

N-[(2'-Methylthio)phenyl] 4-toluenesulfonamide (0.199 g, 0.678 mmol) and 5.5 N potassium hydroxide (20 mL) were heated to reflux in ethanol (10 mL) in a 100-mL round-bottomed flask equipped with a reflux condenser. Dimethyl sulfate (0.20 mL, 2.0 mmol) was added via syringe and the solution was refluxed for one-half hour. The solution was cooled to room temperature, filtered, and the solvent removed under reduced pressure. The remaining water was extracted three times with methylene chloride (50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude solid was recrystallized from ethanol to give 70.6% yield of 137 (0.147 g, 0.478 mmol): mp 126-127°C; IR (KBr) 3080, 2980, 2840, 1480, 1350 and 1160 (S=O, N), 1090, 1050, 820, 770, 580, 560 cm⁻¹; ¹H NMR (CDCl₃) δ 2.40 and 2.43 (2 s, 6 H), 3.1 (s, 3 H), 6.78-7.85 (m, 8 H); ¹³C NMR (CDCl₃) δ 143.59, 141.18, 138.45, 135.72, 129.48, 129.02, 128.24, 127.92, 125.38, 124.73, 38.30, 21.59, 14.76. Anal. Calcd for C₁₅H₁₇NO₂S₂: C, 58.62; H, 5.58; N, 4.56. Found: C, 58.63; H, 5.57; N, 4.55.

N-Methyl-N-[(2'-Methylsulfonyl)phenyl]-4-toluenesulfonamide (133). A solution of N-methyl-N-[(2'-methylthio)phenyl]-4-toluenesulfonamide (11.4 g,
0.0371 mol) and hydrogen peroxide (5 equivalents, 1.5 mL of 33% \( \text{H}_2\text{O}_2 \)) in glacial acetic acid (150 mL) was refluxed for 24 hours. The solution was cooled to room temperature, poured slowly into a beaker of water (200 mL) and then 50 mL of 10% aqueous sodium bicarbonate was gradually poured in. The product was extracted into methylene chloride. The extract was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was recrystallized from ethanol to give 77.1% yield of 133 (9.71 g, 0.0286 mol): mp 194-195°C; IR (KBr) 3080, 3050, 3025, 2990, 2940, 2890, 2825, 1600, 1485, 1350 and 1160 (SO\(_2\)N), 825, 725, 550 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 2.43 (s, 3H), 3.26 (s, 3H), 3.47 (s, 3H), 6.7-8.26 (m, 8H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 144.56, 140.92, 134.74, 134.42, 130.65, 129.93, 129.35, 128.37, 45.07, 40.84, 21.59; mass spectrum, m/e (intensity), 340 (9, M), 324 (137), 307 (68), 274 (68), 260 (100). Anal. Calcd for C\(_{15}\)H\(_{17}\)O\(_4\)N\(_2\): C, 53.09; H, 5.05; N, 4.13. Found: C, 53.36; H, 5.04; N, 4.18.

**Reaction of 133 with Sodium Hydride in THF.** Sodium hydride (6 equivalents, 0.11 g of a 50% oil dispersion) was placed under nitrogen in an oven-dried, round-bottomed flask equipped with a magnetic stirrer. After the sodium hydride was washed several times with hexane via syringe, THF (10 mL) and then sulfonamide 133 (0.20 g, 0.59 mmol) was
The mixture was stirred at room temperature for eighteen hours during which time the reaction was monitored by TLC (ether). D$_2$O (1 mL) was added to quench the reaction. The solution was filtered and the solvent removed under reduced pressure. Methylene chloride (30 mL) was added and the solution was washed with water (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude solid was recrystallized from ethanol to yield 68% of recovered starting material (0.14 g, 0.40 mmol): mp 194-195°C; IR (KBr) 1600, 1485, 1350 and 1160 (SO$_2$N) cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.43 (s, 3H), 3.26 (s, 3H), 3.47 (s, 3H), 6.7-8.26 (m, 8H).

Reaction of 133 with Sodium Hydride in 1,2-Dimethoxyethane at 10°C. The procedure was the same as for the reaction with sodium hydride in THF except that a solution of sulfonamide 133 (0.10 g, 0.29 mmol) in DME (10 mL) was added to sodium hydride (3 equivalents, 0.053 g of a 60% oil dispersion) in DME (20 mL). Both solutions were cooled to 10°C with ice baths. After five hours the reaction was quenched with D$_2$O (0.5 mL). The crude yield of recovered starting material was 0.10 g, mp 192-195°C; after recrystallization from ethanol, mp 194-195°C; IR (KBr) 1600, 1485, 1350 and 1160 (SO$_2$N) cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.43 (s, 3H), 3.26 (s, 3H), 3.47 (s, 3H), 6.7-8.26 (m, 8H).
Reaction of 133 with Sodium Hydride in 1,2-Dimethoxyethane at Room Temperature. The procedure was the same as for the reaction with sodium hydride at 10°C except that a solution of sulfonamide (0.24 g, 0.71 mmol) in DME (10 mL) was added to sodium hydride (3 equivalents, 0.13 g of a 60% oil dispersion) in DME (30 mL) at room temperature. The reaction was monitored by TLC (chloroform). During four hours no change was observed. The reaction was quenched with water. The crude solid was purified by column chromatography (chloroform) to yield recovered starting material (after recrystallization from ethanol) in 80.4% yield (0.194 g, 0.568 mmol): mp 194-195°C; IR (KBr) 1600, 1485, 1350 and 1160 (SO2N) cm⁻¹; ¹H NMR (CDCl₃) δ 2.43 (s, 3H), 3.26 (s, 3H), 3.47 (s, 3H), 6.7-8.26 (m, 8H); and 13.4% yield of 2-(methylamino)phenyl methyl sulfone (141) (0.0176 g, 0.0951 mmol): mp 85-88°C; IR (KBr) 3430 (NH), 1300 and 1140 (SO₂) cm⁻¹; ¹H NMR (CDCl₃) δ 2.87 (s, 3H), 3.02 (s, 3H), 6.13 (br s, 1H), 6.67-7.90 (m, 4H).

Reaction of 133 with Sodium Hydride in 1,2-Dimethoxyethane at 85°C. The procedure was the same as for the reaction with sodium hydride at 10°C except that a solution of sulfonamide 133 (0.243 g, 0.715 mmol in DME (10 mL) was added to sodium hydride (5 equivalents, 0.21 g of a 60% oil dispersion) in DME (15 mL) and the mixture was refluxed at 85°C for one and
one-half hours. TLC (chloroform) showed starting material was still present. The reaction mixture was refluxed for eight hours and then quenched with D₂O (2 mL). The crude solid was purified by column chromatography (chloroform) to give 62.0% of starting material (0.151 g, 0.443 mmol): mp 193-195°C; IR (KBr) 1600, 1485, 1350 and 1160 (SO₂N) cm⁻¹; ¹H NMR (CDCl₃) δ 2.43 (s, 3H), 3.26 (s, 3H), 3.47 (s, 3H), 6.7-8.26 (m, 8H); and a negligible amount of 2-(methylamino)phenyl methyl sulfone (141): IR (KBr) 3430 (NH), 1300 and 1140 (SO₂) cm⁻¹; ¹H NMR (CDCl₃) δ 2.87 (s, 3H), 3.02 (s, 3H), 6.13 (br s, 1H), 6.67-7.90 (m, 4H).

Reaction of 133 with n-Butyllithium. Sulfonamide 133 (0.496 g, 1.45 mmol) was dissolved in dry THF (55 mL) under nitrogen in a flame-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer, thermometer and adapter, and a septum cap. n-Butyllithium (2 equivalents, 1.8 mL of a 1.6 M solution in hexane, 2.9 mmol) was added to the solution via syringe at room temperature. The solution turned an orange-red color immediately. The reaction was monitored by TLC (methylene chloride) and after two hours was quenched with water (1 mL). The solvent was removed under reduced pressure, methylene chloride (50 mL) was added and the solution was washed with saturated sodium chloride (25 mL). The organic layer was dried over anhydrous magnesium
sulfate, filtered, and the solvent removed under reduced pressure. The crude solid was purified by column chromatography (silica gel, methylene chloride) and recrystallized to yield 34.6% of recovered starting material (0.172 g, 0.504 mmol): mp 190-192°C; IR (KBr) 1600, 1485, 1350 and 1160 (SO$_2$N) cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.43 (s, 3H), 3.26 (s, 3H), 3.47 (s, 3H), 6.7-8.26 (m, 8H); and 9.83% yield of 2-(methylamino)phenyl methyl sulfone (141) (0.0266 g, 0.144 mmol): mp 89-91°C; IR (KBr) 3430 (NH), 1330 and 1140 (SO$_2$N) cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.87 (s, 3H), 3.02 (s, 3H), 6.13 (br s, 1 H), 6.67-7.90 (m, 4H).

**Reaction of 133 with Lithium Diisopropylamide.**

Sulfonamide 133 (0.513 g, 1.50 mmol) was dissolved in dry THF (30 mL) under nitrogen in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer and a septum cap. Lithium diisopropylamide (3 equivalents) was prepared in dry THF (20 mL) under nitrogen from diisopropylamine (0.85 mL, 6.0 mmol) and n-butyllithium (2.8 mL of a 1.6 M solution in hexane, 4.5 mmol) in an oven-dried, round-bottomed flask equipped with a magnetic stirrer and septum cap. The solution of LDA was cannulated into the solution of the sulfonamide via a double-tipped needle at room temperature. The reaction was monitored by TLC (methylene chloride) and after three hours, was quenched with water (1 mL). The solution was
filtered and the solvent removed under reduced pressure. Water was added to the residual oil and the mixture was extracted four times with ethyl acetate (100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude solid was purified by column chromatography (methylene chloride, and then ethyl acetate) to yield 11.4% recovered starting material (0.0585 g, 0.172 mmol): mp 190-192°C; IR (KBr) 1600, 1485, 1350 and 1160 (SO₂N) cm⁻¹; ¹H NMR (CDCl₃) 2.43 (s, 3H), 3.26 (s, 3H), 3.47 (s, 3H), 6.7-8.26 (m, 8H); and 41.5% yield of 2-(methylamino)phenyl methyl sulfone (141) (0.116 g, 0.627 mmol): mp 90-92°C; IR (KBr) 3430 (NH), 1300 and 1140 (SO₂) cm⁻¹; ¹H NMR (CDCl₃) 2.87 (s, 3H), 3.02 (s, 3H), 6.13 (br s, 1H), 6.67-7.90 (m, 4H). The filtered solid (from the THF) was dried under vacuum and was identified as 4-toluenesulfinic acid by matching it's proton NMR spectrum with that of an authentic sample. The yield of 4-toluenesulfinic acid was 33.1% (0.0809 g, 0.499 mmol).

2-Acetamidophenyl Methyl Sulfide (142).

2-Aminothioanisole (7.50 g, 0.0540 mol) was dissolved in chloroform (100 mL) in a 250-mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser and an addition funnel. Triethylamine (11.2 mL, 0.0810 mol) was added dropwise followed by acetic anhydride (10.2 mL, 0.108
mol) from another addition funnel. The solution was stirred at room temperature for one hour and then refluxed for one hour. The solution was cooled to room temperature, washed with water (25 mL), dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure. The crude solid was recrystallized from cyclohexane to give 90.4% yield of 142 (8.88 g, 0.0488 mol): mp 101-103°C; IR (KBr) 3220 (NH), 3020, 3000, 2920, 1650 (C=O), 1570, 1540 (amide II band), 745, 550 cm⁻¹; ¹H NMR (CDCl₃) δ 2.23 (s, 3H), 2.38 (s, 3H), 6.98-8.36 (m, 5H); ¹³C NMR (CDCl₃) δ 168.43, 138.19, 132.53, 128.63, 125.51, 124.53, 120.96, 24.71, 18.73. Anal. Calcd for C₉H₈NOS: C, 59.65; H, 6.12; N, 7.73. Found: C, 59.64; H, 6.22; N, 7.84.

2-Acetamidophenyl Methyl Sulfone (143).

2-Acetamidophenyl methyl sulfide (7.80 g, 0.0430 mol) was dissolved in acetic acid (200 mL) in a 500-mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser. Hydrogen peroxide (2.5 mL, 0.43 mol) was added and the solution was refluxed for ten days. The reaction was monitored by TLC (ethyl acetate). Even though a small amount of sulfoxide was still present, the reaction was quenched by cooling and pouring into a beaker containing 200 mL of water. The aqueous solution was extracted five times with methylene chloride (250 mL) and the combined organic extracts were washed three times with water (90 mL).
and three times with 10% aqueous sodium bicarbonate (90 mL). The solution was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude solid was purified by column chromatography (ethyl acetate) and then by recrystallization from carbon tetrachloride to yield 53.1% 143 (4.86 g, 0.0229 mol):
mp 144-145°C; IR (KBr) 3320 (NH), 3020, 2930, 1685 (C=O), 1510, 1300 and 1145 (SO₂), 960, 780, 755, 670 cm⁻¹; ¹H NMR (CDCl₃) δ 2.13 (s, 3H), 2.98 (s, 3H), 7.02-8.00 (m, 9H), 9.97 (br s, 1H); ¹³C NMR (CDCl₃) δ 168.62, 137.08, 135.39, 129.28, 127.07, 124.21, 122.97, 44.29, 25.10; mass spectrum, m/e (intensity), 215 (39, M+2), 214 (80, M+1), 213 (597, M), 171 (1000), 156 (453), 108 (886), 92 (1000). Anal. Calcd for C₉H₆NO₃S: C, 50.69; H, 5.20; N, 6.57. Found: C, 50.54; H, 5.17; N, 6.58.

2-Aminophenyl Methyl Sulfone (144).
2-Acetamidophenyl methyl sulfone (0.329 g, 1.52 mmol) was dissolved in hot ethanol (20 mL) in a 100-mL round-bottomed flask equipped with a reflux condenser. Aqueous sodium hydroxide (2 mL of 5N solution) was added and the solution refluxed for eight hours. The reaction was monitored by TLC (ethyl acetate). The solvent was removed under reduced pressure. The residue was dissolved in chloroform (30 mL), washed three times with water (30 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed under
reduced pressure. The solid was recrystallized from carbon tetrachloride to yield 85.9% of 144 (0.223 g, 1.31 mmol): mp 83°C; IR (KBr) 3460 and 3370 (NH\textsubscript{2}), 3010, 2925, 1630, 1490, 1460, 1300 and 1140 (SO\textsubscript{2}), 960, 750 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 3.03 (s, 3H), 5.20 (br s, 2H), 6.68-7.82 (m, 4H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) 146.38, 135.13, 129.28, 121.93, 117.84, 117.71, 42.27. Anal. Calcd for C\textsubscript{14}H\textsubscript{10}N\textsubscript{2}O\textsubscript{2}S: C, 49.09; H, 5.30; N, 8.19. Found: C, 49.09; H, 5.25; N, 8.16.

2-(Methylamino)phenyl Methyl Sulfone (141).

\textsuperscript{N}-Monomethylation of 2-aminophenyl methyl sulfone was accomplished by following Krishnamurthy's procedure\textsuperscript{47} of formylation of the amine group using acetic formic anhydride followed by in situ reduction of the generated formamide using borane:methyl sulfide complex.

2-Aminophenyl methyl sulfone (0.979 g, 5.72 mmol) was thus converted to 141 in 89.4% yield (0.943 g, 5.10 mmol): mp 91-92°C; IR (KBr) 3430 (NH), 3080, 3020, 2920, 2880, 2820, 1615, 1575, 1520, 1475, 1330, 1300 and 1140 (SO\textsubscript{2}), 955, 755 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 2.87 (s, 3H), 3.02 (s, 3H), 6.13 (br s, 1H), 6.67-7.90 (m, 4H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) 147.82, 135.46, 129.67, 121.35, 116.08, 111.79, 42.27, 29.98. Anal. Calcd for C\textsubscript{17}H\textsubscript{13}NO\textsubscript{2}S: C, 51.88; H, 5.99; N, 7.57. Found: C, 52.08; H, 6.02; N, 7.70.

2'-Formylphenyl 4-Toluenesulfonate (148).\textsuperscript{61} In
a 500-mL Erlenmeyer flask, salicyaldehyde (21.3 mL, 24.4 g, 0.200 mol) and pyridine (30 mL) were mixed together. 4-Toluenesulfonyl chloride (1.5 equivalents, 57.1 g, 0.300 mol) was added through a powder funnel. The mixture was agitated several times during the six hour reaction time, during which a solid precipitated until finally the mixture was a solid cake. Cyclohexane was added to the reaction mixture, which was brought to boiling and then decanted. The product crystallized to yield 85.5% of 148 (47.5 g, 0.171 mol): mp 62.5-64°C (lit. mp 63-64°C); IR (KBr) 3080, 3040, 2920, 2890, 2760 (CHO), 1699 (C=O), 1605, 1380 and 1190 (SO2O), 1180, 865, 785 cm⁻¹; ¹H NMR (CDCl₃) δ 2.4 (s, 3H), 7.1-7.93 (m, 8H), 10.06 (s, 1H).

2'-(N-Methylformiminyl)phenyl 4-Toluenesulfonate (149). 2'-Formylphenyl 4-toluenesulfonate (40.7 g, 0.147 mol) was dissolved in methanol (800 mL) in a 2-liter round-bottomed flask equipped with a magnetic stirrer. Aqueous methylamine solution (6 equivalents, 12 mL of a 40% solution) was added and the mixture was stirred for twelve hours. The solvent was removed under reduced pressure and the crude solid recrystallized from cyclohexane to give 89.1% yield of 149 (37.9 g, 0.131 mol): mp 80-81°C; IR (KBr) 3070, 3050, 3020, 2945, 2905, 2890, 2850, 2780, 1650 (C=N), 1600, 1485, 1450, 1380 and 1190 (SO2O), 1180, 1165, 1090, 880, 770 cm⁻¹; ¹H NMR (CDCl₃) δ 2.43 (s, 3H), 3.30 (s, 3H), 7.06-7.95 (m, 8H), 8.15 (s, 1H);
$^{13}$C NMR (CDCl$_3$) $\delta$ 156.40, 148.79, 145.80, 132.08, 131.36, 129.93, 129.54, 128.50, 127.59, 127.33, 123.30, 48.25, 21.65. Anal. Calcd for C$_{15}$H$_{15}$NO$_3$S: C, 62.27; H, 5.23; N, 4.84. Found: C, 62.53; H, 5.22; N, 4.83.

2'-((N-Methylaminomethyl)phenyl 4-Toluene-sulfonate (147). Sodium borohydride (2.4 equivalents, 0.782 g, 0.0207 mol) was added gradually through a powder funnel to a solution of imine 149 (2.50 g, 8.65 mmol) in dry methanol (150 mL). The solution effervesced during the addition. The solution was stirred for twelve hours and the reaction was monitored for the disappearance of starting material by TLC (ethyl acetate). The solvent was removed under reduced pressure and the residual oil was dissolved in ethyl acetate (100 mL). The solution was washed with 10% aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The brown oil was transferred to a 25-mL round-bottomed flask and distilled in a kugelrohr apparatus (160°C, 0.2 mm) to give 80.1% of 147 (2.02 g, 6.93 mmol): IR (neat, NaCl plates) 3345 (NH), 3080, 3040, 2945, 2860, 1610, 1495, 1460, 1380 and 1200 (SO$_2$O), 1160, 1085, 870, 775 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.35 (s, 1H), 2.34 (s, 3H), 2.44 (s, 3H), 3.57 (s, 2H), 7.10-7.93 (m, 8H); $^{13}$C NMR (CDCl$_3$) $\delta$ 147.88, 145.54, 133.57, 132.92, 130.39, 129.87, 128.30, 127.98, 127.13, 122.19,
49.81, 35.96, 21.65; mass spectrum, m/e (intensity), 291 (80, M), 276 (47), 155 (53), 136 (1000), 120 (158), 91 (410). Anal. Calcd for C₁₅H₁₇NO₃S: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.47; H, 6.00; N, 4.72.

Reaction of 147 with n-Butyllithium.

2'-{(N-Methylaminomethyl)phenyl 4-toluenesulfonate (0.192 g, 0.660 mmol) was dissolved in THF (30 mL) under nitrogen in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer, septum cap and a nitrogen inlet and outlet. The solution was brought to -73°C with a Dry Ice-acetone bath. n-Butyllithium (4 equivalents, 1.6 mL of a 1.6 M solution in hexane, 2.6 mmol) was added via syringe. The solution turned immediately to a red-brown color. The reaction was monitored by TLC (ethyl acetate) which showed five spots initially, which were unchanged for three and one-half hours. The reaction was quenched at -78°C with water (0.3 mL) and then allowed to warm to room temperature. The THF was removed under reduced pressure, and ethyl acetate (30 mL) was added. The solution was washed with water (10 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. An attempt was made to purify the crude yellow oil by preparative plate chromatography (ethyl acetate). Each of the five bands which were separated consisted of two to seven spots by TLC (chloroform). No further work was attempted on this
Reaction of 147 with Lithium Diisopropylamide at -78°C. Sulfonate ester 147 (0.533 g, 1.33 mmol) was dissolved in dry THF (30 mL) under nitrogen in an oven-dried, round-bottomed flask equipped with a magnetic stirrer, a septum cap and a nitrogen inlet and outlet. Lithium diisopropylamide (3 equivalents) was prepared in dry THF (20 mL) under nitrogen from diisopropylamine (1.13 mL, 8.08 mmol and n-butyllithium (3.6 mL of a 1.6 M solution in hexane, 6.1 mmol) in an oven-dried, round-bottomed flask equipped with a magnetic stirrer and a septum cap. Both solutions were brought to -73°C with Dry Ice-acetone baths. The solution of LDA was cannulated into the solution of the sulfonate ester via a double-tipped needle. TLC (0.6 hexane : 0.4 ethyl acetate) five minutes after the addition showed one compound and a baseline spot. The TLC was unchanged after twenty minutes. The reaction was quenched at -78°C with aqueous ammonium chloride solution, and then was allowed to warm to room temperature. The THF was removed under reduced pressure, methylene chloride (50 mL) was added and the solution was washed with water (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. Preparative plate chromatography (ethyl acetate) was done on the crude material to yield three bands. One band was a very small amount of a highly colored
oil which was not identified. Another band was shown by mass spectrometry to consist of many compounds. No further work was done on this band. The third band was repurified by column chromatography (chloroform) to yield the rearranged product, \( N\)-2'-hydroxybenzyl-\( N\)-methyl-4-toluenesulfonamide (151), in 32.81% yield (0.175 g, 0.601 mmol): mp 91-93°C; IR (KBr) 3410 (OH), 3080, 3040, 2990, 2930, 2880, 1600, 1460, 1325 and 1150 (SO2N), 1080, 915, 815, 750 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 2.45 (s, 3 H), 2.66 (s, 3 H), 4.06 (s, 2 H), 6.81-7.85 (m, 9 H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 155.88, 144.17, 133.31, 130.45, 130.26, 130.06, 127.65, 120.07, 120.01, 117.18, 51.31, 34.40, 21.59; mass spectrum, m/e (intensity) 291 (99, M), 185 (195), 155 (204), 136 (192), 91 (1000).

Anal. Calcd for C\(_{15}\)H\(_{17}\)NO\(_3\)S: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.61; H, 5.91; N, 4.70.

\((2'\text{-Formylphenyl})\) 4-\(d_3\)-Methylbenzenesulfonate (154). Sulfonate ester 154 was prepared according to the procedure for the nondeuterated analog 148 except that salicylaldehyde (2 equivalents, 0.82 mL, 7.7 mmol) was coupled with 4-\(d_3\)-methylbenzenesulfonyl chloride (0.739 g, 3.83 mmol). Excess salicylaldehyde was removed at the end of the reaction by kugelrohr distillation. The product was purified by recrystallization from cyclohexane to yield 83.1% 154 (0.887 g, 3.13 mmol): mp 59-61°C (lit. 61°C 63-64°C); IR (KBr) 3080, 3040, 2890, 2870,
2760 (CHO), 1975 and 1950 (CD), 1695 (C=O), 1605, 1480, 1395, 1380 and 1135 (SO₂O), 1280, 1180, 1160, 1085, 865, 785, 645, 560, 545 cm⁻¹; \(^1\)H NMR (CDCl₃) \(\delta\) 7.13-7.96 (m, 8H), 10.06 (s, 1H); \(^1\)³C NMR (CDCl₃) \(\delta\) 187.29, 151.26, 136.19, 135.26, 131.56, 130.13, 123.35, 128.70, 128.52, 127.52, 123.75; mass spectrum, m/e (intensity) 230 (27, M+1), 279 (113, M), 278 (115), 277 (16).

\(\alpha'-d_1-2'-(\text{N-Methylaminomethyl})\text{phenyl}\)

\(4-d_3\)-Methylbenzenesulfonate (153). Sulfonate ester 153 was prepared from 155 (0.887 g, 3.18 mmol) and aqueous methylamine solution according to the procedure for the nondeuterated analog 149. The \(^1\)H NMR spectrum showed the imine CH peak at 8.15 ppm and the N-methyl at 3.33 ppm. Without further purification, the imine was reduced with sodium borodeuteride (1.5 equivalents, 0.199 g, 4.76 mmol, Aldrich) in methanol (50 mL) according to the procedure for the synthesis of the nondeuterated analog 151. The crude product was purified by column chromatography (silica gel, ethyl acetate) to yield 74.4% 153 (0.698 g, 2.37 mmol): IR (neat, NaCl plates) 3340 (NH), 3070, 3040, 2980, 2940, 2120 (CD), 1930 (CD), 1600, 1580, 1485, 1450, 1370 and 1135 (SO₂O), 1155, 1080, 865, 780 cm⁻¹; \(^1\)H NMR (CDCl₃) \(\delta\) 1.66 (br s, 1H), 2.33 (s, 3H), 3.55 (br s, 1H), 7.06-7.35 (m, 8H); \(^1\)³C NMR (CDCl₃) \(\delta\) 147.34, 145.50, 133.05, 132.79, 130.51,
Crossover reaction of 147 and 153 (0.05 M solution) with Lithium Diisopropylamide. Equimolar amounts of the sulfonate esters 147 (0.144 g, 0.495 mmol) and 153 (0.146 g, 0.495 mmol) were dissolved in dry THF (20 mL) in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer, septum cap and a nitrogen inlet and outlet. Lithium diisopropylamide (LDA) (3 equivalents, 3.0 mmol) was prepared in dry THF (20 mL) under nitrogen from diisopropylamine (0.44 mL, 3.9 mmol) and n-butyllithium (1.8 mL of a 1.6 M solution in hexane, 3.0 mmol) in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer and septum cap. Both solutions were brought to -78°C with Dry Ice-acetone baths. The solution of LDA was cannulated into the solution of the sulfonate esters via a double-tipped needle. The reaction was monitored by TLC (3 hexane : 2 ethyl acetate). The reaction was quenched after fifteen minutes with methanol (10 mL) to which two drops of sulfuric acid had been added. The solution was allowed to warm to room temperature, filtered, and the solvent was removed under reduced pressure. The crude product was purified by preparative plate chromatography (3 hexane : 2 ethyl
acetate) to yield 20.9% of the rearranged product (0.0605 g): mp 90-93°C (mp of 151 is 91-93°C); IR (KBr) 3330 (OH), 3070, 3040, 2980, 2930, 1925 (CD), 1810 (CD), 1600, 1495, 1460, 1330 and 1160 (SO₂N), 1290, 1090, 920, 820, 750 cm⁻¹; ¹H NMR (CDCl₃)  auction 2.45 (s, 1.6H), 2.66 (s, 3H), 4.06 (s, 1.4H), 6.81-7.85 (m, 9H); ¹³C NMR (CDCl₃) auction 155.88, 144.17, 133.31, 130.45, 130.26, 130.00, 127.65, 120.11, 117.18, 51.31, 34.40, 21.59; mass spectrum, m/e (intensity) 295 (185), 294 (243), 293 (122), 292 (222), 291 (228).

Crossover reaction of 147 and 153 (0.0051 M solution) with Lithium Diisopropylamide. The procedure was the same as for the previous crossover reaction except that a 0.00509 M solution of 147 (0.0429 g, 0.148 mmol) and 153 (0.0435 g, 0.148 mmol) in dry THF (50 mL) was treated with a solution of LDA (3 equivalents, 0.443 mmol) in dry THF (10 mL) at room temperature. The reaction was quenched after fifteen minutes with 10% aqueous sulfuric acid solution (10 mL). The crude product was purified by column chromatography (silica gel, methylene chloride) to yield 14.4% of the rearranged product (0.0124 g): mp 90-92°C (mp of 151 is 91-93°C); IR (KBr) 3330 (OH), 1925 (CD), 1810 (CD), 1330 and 1160 (SO₂N) cm⁻¹; ¹H NMR (CDCl₃) auction 2.45 (s, 2.5H), 2.66 (s, 3H), 4.06 (s, 1H), 6.81-7.85 (m, 9H); ¹³C NMR (CDCl₃) auction 130.32, 130.03, 127.65, 120.08, 117.28, 51.41,
34.40, 21.58; mass spectrum, m/e (intensity) 295 (11), 294 (147), 293 (151), 292 (48), 291 (188).

**N-Methyl-benzene-4-toluenedisulfonimide (160).**

Preparation of the disulfonimide 160 was accomplished by following Baumgarten's procedure for the generation of the sodium salt of N-methyl-4-toluenesulfonamide (37.2 g, 0.201 mol) with sodium hydride in DMF followed by treatment of this soluble sodium salt with benzenesulfonyl chloride (1 equivalent). The product was recrystallized from ethanol twice to give 81.1% 160 (52.9 g, 0.163 mol): mp 91-93°C (lit. mp 92-93°C); IR (KBr) 3060, 2950, 2920, 1600, 1455, 1370 and 1170 (SO₂N-SO₂), 1080 (CS), 820, 730, 680 cm⁻¹; ¹H NMR (CDCl₃) δ 2.42 (s, 3H), 3.27 (s, 3H), 7.27-8.13 (m, 9H); ¹³C NMR (CDCl₃) δ 145.02, 139.23, 136.17, 133.83, 129.74, 129.09, 127.85, 126.94, 34.73, 21.59. Anal. Calcd for C₁₅H₁₅NO₄S₂: C, 51.67; H, 4.64; N, 4.30. Found: C, 52.02; H, 4.67; N, 4.33.

**Reaction of 160 with n-Butyllithium at -78°C.** The disulfonimide 160 (3.00 g, 9.22 mmol) was dissolved in dry THF (50 mL) under nitrogen in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer, septum cap and a nitrogen inlet and outlet. The solution was cooled to -78°C with a Dry Ice-acetone bath. n-Butyllithium (2 equivalents, 11 mL of a 1.6 M solution in hexane, 0.18 mmol) was added to the
solution via syringe; the solution turned a blackish-red color. The reaction was monitored by TLC (chloroform). The reaction was quenched after one hour with water (3 mL) and then it was allowed to warm to room temperature. The THF was removed under reduced pressure and the remaining water was extracted three times with methylene chloride (30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude oil was purified by column chromatography (silica gel, chloroform) to yield two impure fractions along with many unresolved bands. The two impure substances were repurified by preparative plate chromatography (chloroform) to yield 22.5% recovered starting material 160 (0.676 g, 2.08 mmol): mp 90-92°C (lit. mp 92-93°C); IR (KBr) 1370 and 1170 (SO₂NSO₂) cm⁻¹; ¹H NMR (CDCl₃) δ 2.42 (s, 3H), 3.27 (s, 2H), 7.27-8.13 (m, 9H); and 1.73% of N-methyl-4-toluenesulfonamide (161) (0.0296 g, 0.159 mmol): mp 74-76°C (lit. mp 76-79°C); IR (KBr) 3280 (NH), 3050, 2960, 2920, 2860, 1590, 1440, 1320 and 1150 (SO₂), 1080, 830, 820, 710, 680 cm⁻¹; ¹H NMR (CDCl₃) δ 2.50 (s, 3H), 2.63 (d, 3H), 4.50 (br s, 1H), 7.25-7.80 (m, 4H); ¹³C NMR (CDCl₃) δ 135.91, 132.66, 129.74, 127.26, 29.33, 21.53.

Reaction of 160 with n-Butyllithium at Room Temperature

The reaction procedure was the same as for
the reaction at -78°C except that the disulfonimide 160 (1.14 g, 3.49 mmol) was treated with n-butyllithium (3 equivalents, 6.5 mL of a 1.6 M solution in hexane, 0.010 mol) at room temperature. The crude product was purified by column chromatography (silica gel, chloroform) to yield 5.92% 160 (0.0672 g, 0.206 mmol); IR (KBr) 1370 and 1170 (SC\_\text{SO}_2), 1080 (CS) cm\(^{-1}\); \(^1\text{H NMR (CDCl}_3\) 2.4 (s, 3H), 3.3 (s, 3H), 7.3-8.1 (m, 9H); and 27.7% of N-methyl-4-toluenesulfonamide (161) (0.170 g, 0.965 mmol): IR (KBr) 3280 (NH), 1320 and 1150 (\text{SO}_2\_\text{N}) cm\(^{-1}\); \(^1\text{H NMR (CDCl}_3\) 2.50 (s, 3H), 2.62 (d, 3H), 4.50 (br s, 1H), 7.25-7.80 (m, 4H).

\textbf{N-Methyl-Benzencesulfonamide (167). Method 1:} Potassium hydroxide (22.1 g, 1.58 mol) and aqueous methylamine solution (1.5 equivalents, 5.4 mL of a 40% solution) were dissolved in water (100 mL) in a 500-mL round-bottomed flask equipped with a magnetic stirrer and a pressure-equalizing addition funnel. Benzenesulfonyl chloride (33.5 mL, 0.263 mol) was added slowly. The addition funnel was exchanged for a reflux condenser and the mixture was heated in a hot water bath at 80°C for two hours. The pH of the solution was monitored and kept basic through the addition of aqueous potassium hydroxide solution (10%). The solution was cooled to room temperature and the precipitate filtered. The solid was recrystallized
from ethanol to yield 22.2% of

**N-methyl-bis-benzenedisulfonimide (166)** (9.09 g, 0.292 mol): mp 110-111°C (lit. mp 111-112°C);

IR (KBr) 3080, 3020, 2960, 1590, 1460, 1380 and 1180 (SO$_2$NSO$_2$), 1090 (CS), 335 (SNS), 720, 690 cm$^{-1}$;

$^1$H NMR (CDCl$_3$) $\delta$ 3.26 (s, 3 H), 7.5-8.1 (m, 10H);

$^{13}$C NMR (CDCl$_3$) $\delta$ 139.17; 133.90, 129.09, 127.92, 34.79; mass spectrum, m/e (intensity) 311 (46, M), 247 (71), 170 (18), 156 (154), 143 (117), 142 (120), 141 (537), 78 (144), 77 (1000). Anal. Calcd for C$_{13}$H$_{13}$NO$_4$S$_2$: C, 50.15; H, 4.20; N, 4.50.

Found: C, 50.44; H, 4.15; N, 4.55. The basic water filtrate was neutralized with aqueous sulfuric acid solution (10%) and extracted three times with methylene chloride (300 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield 25.2% **167** (11.3 g, 0.0661 mol): bp 135°C, 0.1mm (lit. bp 202°C, 17 mm); IR (neat, NaCl plates) 3300 (NH), 3080, 3000, 2960, 2920, 1480, 1455, 1325 and 1170 (SO$_2$N), 1100, 1080, 840, 760 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.63 (d, 3H), 4.63 (br s, 1H), 7.23-7.95 (m, 5H); $^{13}$C NMR (CDCl$_3$) $\delta$

138.58, 132.54, 123.96, 127.01, 29.07; mass spectrum, m/e (intensity) 173 (71, M+2), 172 (137, M+1), 171 (1000, M), 141 (778), 125 (170), 106 (396), 94 (229), 77 (1000).

**Method 2:** A phase-transfer procedure was employed
where potassium hydroxide (22.1 g, 1.58 mol) and aqueous methylamine solution (1.5 equivalents, 5.4 mL of a 40% solution) were dissolved in water (70 mL) in a 500-mL round-bottomed flask equipped with a magnetic stirrer and a pressure-equalizing addition funnel. A solution of benzenesulfonyl chloride (35 mL, 0.27 mol) in ether (100 mL) was added slowly. The mixture was stirred for twelve hours. The ether layer was separated from the aqueous layer. The aqueous layer was extracted five times with ether (400 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a liquid (17.9 g). By integration of the methyl peaks in the proton NMR, the composition was calculated to be 79.4% 167 and 20.5% 166. The water was acidified and reextracted three times with ether (90 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield 167 (7.09 g): IR (KBr) 3300 (NH), 1325 and 1170 (SO₂N) cm⁻¹; ¹H NMR (CDCl₃) 6 2.63 (d, 3H), 4.63 (br s, 1H), 7.23-7.75 (m, 5H). The total yield of 167 was 45.3% (21.3 g, 0.124 mol). The yield of 166 based on the ¹H NMR data was 8.96% (3.66 g, 0.0118 mol).

**N-Methyl-bis-benzenedisulfonimide (166)**

Preparation of the disulfonimide 166 was accomplished by following Baumgarten's procedure of the
generation of the sodium salt of 167 (17.0 g, 0.0993 mol) with sodium hydride in DMF followed by treatment of this soluble sodium salt with benzenesulfonyl chloride (1.5 equivalents, 19.0 mL, 0.149 mol). The product was recrystallized from ethanol to give 39.1% yield of 166 (12.1 g, 0.0388 mol): mp 111-112°C (lit.66 mp 111-112°C); IR (KBr) 1380 and 1130 (SO₂NSO₂) cm⁻¹; ¹H NMR (CDCl₃) δ 3.26 (s, 3H), 7.5-8.1 (m, 10 H).

Reaction of 166 with n-Butyllithium (2 equivalents). Disulfonimide 166 (0.522 g, 1.68 mmol) was dissolved in dry THF (50 mL) under nitrogen in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer, septum cap and a nitrogen inlet and outlet. n-Butyllithium (2 equivalents, 2.1 mL of a 1.6 M solution in hexane, 3.3 mmol) was added to the solution via syringe. The solution turned brown immediately. The reaction was monitored by TLC (methylene chloride). During one and one-half hours no change was observed. The reaction was quenched with water (10 mL) and the THF was removed under reduced pressure. The remaining aqueous mixture was extracted three times with methylene chloride (60 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (silica gel, methylene
chloride) to give 44.6% recovered starting material 166 (0.233 g, 0.749 mmol): mp 109-111°C (lit. 111-112°C); IR (KBr) 1380 and 1180 (SO₂NSO₂) cm⁻¹; ¹H NMR (CDCl₃)  δ 3.26 (s, 3H), 7.5-8.1 (m, 10H); 28.7% of N-methyl benzenesulfonamide (167) (0.0823 g, 0.481 mmol): IR (NaCl plates) 3300 (NH), 1325 and 1170 (SO₂N) cm⁻¹; ¹H NMR (CDCl₃)  δ 2.63 (d, 3H), 4.63 (br s, 1H), 7.23-7.75 (m, 5H); and 22.0% phenyl n-butyl sulfone (168) (0.0731 g, 0.369 mmol): bp 165-167°C (lit. 165-170°C, 1mm); IR (neat, NaCl plates) 3080, 2980, 2950, 2890, 1590, 1455, 1320 and 1150 (SO₂), 1090, 730, 690, 600 cm⁻¹; ¹H NMR (CDCl₃)  δ 0.90 (t, 3H), 1.20-1.83 (m, 4H), 3.10 (t, 2H), 7.40-7.96 (m, 5H); ¹³C NMR (CDCl₃)  δ 139.30, 133.60, 129.25, 128.01, 56.09, 24.65, 21.53, 13.49; mass spectrum, m/e (intensity) 199 (21, M+1), 198 (150, M), 143 (1000), 142 (360), 134 (103), 133 (286), 132 (341), 125 (204), 105 (482), 57 (938).

Reaction of 166 with n-Butyllithium (3 equivalents). The procedure was the same as for the reaction with 2 equivalents of n-butyllithium except that 166 (1.01g, 3.23 mmol) was treated with n-butyllithium (3 equivalents, 6.0 mL of a 1.6 M solution in hexane, 9.7 mmol). The crude material was purified by column chromatography (silica gel, methylene chloride) to give 1.5% yield of recovered starting material.
166 (0.015 g, 0.048 mmol): IR (KBr) 1380 and 1180 (SO₂NSO₂) cm⁻¹; ¹H NMR (CDCl₃) δ 3.26 (s, 3H), 7.5-8.1 (m, 10H); 42.9% yield of 167 (0.237 g, 1.38 mmol): IR (neat, NaCl plates) 3300 (NH), 1325 and 1170 (SO₂N) cm⁻¹; ¹H NMR (CDCl₃) δ 2.63 (d, 3H), 4.63 (br s, 1H), 7.23-7.75 (m, 5H); and 29.4% yield of 168 (0.188 g, 0.947 mmol): IR (neat, NaCl plates) 1320 and 1150 (SO₂) cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (t, 3H), 1.20-1.83 (m, 4H), 3.10 (t, 2H), 7.40-7.96 (m, 5H); mass spectrum m/e 198 (M).

**N-Phenyl-4-toluenesulfonamide.** Aniline (15.0 mL, 0.165 mol) was dissolved in methylene chloride (300 mL) in a 500-mL round-bottomed flask equipped with a magnetic stirrer. Pyridine (13.3 mL, 0.165 mol) and then 4-toluenesulfonyl chloride (31.4 g, 0.165 mol) were added successively. A water bath was used to absorb the heat of the reaction. After being stirred for one-half hour, the solution was washed three times with water (300 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The product was purified by short funnel chromatography (silica gel type 60, for TLC, methylene chloride) and then by recrystallization from ethanol to give 78.7% N-phenyl-4-toluenesulfonamide (32.0 g, 0.13 mol): mp 94-95.5°C (lit.76 mp 103°C), IR (KBr) 3240
(NH), 3090, 3050, 3020, 2960, 2900, 1600, 1490, 1470, 1410, 1340 and 1150 (SO₂N), 1320, 1290, 1190, 1090, 900, 810, 700, 560 cm⁻¹; \(^1\)H NMR (CDCl₃) \(\delta\) 2.33 (s, 3H), 6.93-7.70 (m, 9H); \(^1^3\)C NMR (CDCl₃) \(\delta\) 143.78, 136.63, 136.11, 129.61, 129.22, 127.26, 125.18, 121.41, 21.46.


\_N-Methyl-\_N-phenyl-4-toluenesulfonamide (170). N-Phenyl-4-toluenesulfonamide (10.0 g, 0.0405 mol) and potassium hydroxide (2.27 g, 0.0405 mol) were dissolved in ethanol (150 mL) in a 500-mL round-bottomed flask equipped with a magnetic stirrer. Iodomethane (3 equivalents, 7.5 mL, 0.12 mol) was added to the solution. The reaction was monitored by TLC (methylene chloride). During three days the TLC remained unchanged; a small amount of starting material was always present. The solvent was removed under reduced pressure, ethyl acetate (60 mL) was added and the solution was washed two times with water (40 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was recrystallized twice from ethanol to yield 86.8% 170 (9.18 g, 0.0352 mol): mp 92-93°C (lit. 62 mp 94°C); IR (KBr) 3060, 2900, 1590, 1480, 1340 and 1160 (SO₂N), 1140, 1080, 1050, 850, 790, 700, 640, 550 cm⁻¹; \(^1\)H NMR
(CDCl$_3$) $\delta$ 2.43 (s, 3H), 3.18 (s, 3H), 7.00-7.50 (m, 9H); $^{13}$C NMR (CDCl$_3$) $\delta$ 143.52, 141.70, 133.70, 129.35, 128.83, 127.92, 127.26, 126.68, 38.11, 21.52; mass spectrum, m/e (intensity) 263 (37, M+2), 262 (103, M+1), 261 (593, M), 197 (232), 156 (110), 106 (1000), 91 (393). Anal. Calcd for C$_{14}$H$_{15}$N$_2$O$_2$S: C, 64.43; H, 5.79; N, 5.36. Found: C, 64.23; H, 5.72; N, 5.32.

**Reaction of 170 with n-Butyllithium.**

Sulfonamide 170 (1.01 g, 3.86 mmol) was dissolved in dry THF (15 mL) under nitrogen in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer, septum cap and a nitrogen inlet and outlet. A water bath was used to absorb the heat of the reaction. n-Butyllithium (2 equivalents, 4.8 mL of a 1.6 M solution in hexane, 7.7 mmol) was added all at once via syringe. The solution turned brown immediately. The reaction was monitored by TLC (chloroform) and after fifteen minutes, all the starting material was gone. The reaction was quenched with water (3 mL), and the THF was removed under reduced pressure. The remaining aqueous mixture was extracted three times with ethyl acetate (90 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude solid was recrystallized from ethanol and then from methanol to yield 29.7% (2-Methylamino)phenyl 4-tolyl sulfone (171) (0.300 g, 1.15 mmol): mp
135-136°C (lit. mp 134-135°C); IR (KBr) 3400 (NH), 3040, 2895, 2800, 1600, 1560, 1460, 1325, 1285 and 1140 (SO₂), 1080, 800, 760, 640, 560, 510 cm⁻¹;

¹H NMR (CDCl₃) ∆ 1.55 (s, 1H), 2.38 (s, 3H), 2.82 (s, 3H), 6.13-7.90 (m, 8H); ¹³C NMR (CDCl₃) ∆ 147.88, 143.78, 139.17, 135.20, 130.32, 129.61, 126.81, 121.61, 115.89, 111.72, 30.04, 21.53; mass spectrum, m/e (intensity) 263 (106, M+2), 262 (307, M+1), 261 (1000, M), 197 (194), 196 (728), 182 (622), 106 (255), 105 (1000), 91 (349), 78 (517), 77 (690). Anal. Calcd for C₁₄H₁₅NO₂S: C, 64.43; H, 5.79; N, 5.36. Found: C, 64.20; H, 5.69; N, 5.32.

N-d₃-Methyl-N-phenyl-4-d₃-methylbenzene-sulfonamide (172). Aniline (1.1 equivalents, 0.17 mL, 1.8 mmol) was coupled to 4-d₃-methylbenzenesulfonyl chloride (0.321 g, 1.66 mmol) according to the procedure for the synthesis of N-phenyl-4-toluenesulfonamide. The crude product was purified by column chromatography (silica gel, methylene chloride) to yield N-phenyl-4-d₃-methylbenzenesulfonamide: IR (KBr) 3260 (NH), 3020, 2960, 2860, 1920 (CD), 1600, 1490, 1400, 1340 and 1150 (SO₂N), 1320, 1270, 1080, 910, 750, 570, 550 cm⁻¹; ¹H NMR (CDCl₃) ∆ 2.33 (br s, 0.2 H), 3.55 (br s, 1H), 6.93-7.70 (m, 9H). Without further purification, the sulfonamide was dissolved in ethanol (50
mL), and potassium hydroxide (2 equivalents, 0.19 g, 3.3 mmol) and then d\textsubscript{3}-iodomethane (0.22 mL, 3.3 mmol, Aldrich) were added according to the procedure for the synthesis of the nondeuterated analog 170. The crude product was purified by column chromatography (silica gel, methylene chloride) to yield 45% 172 (0.20 g, 0.75 mmol): mp 89-91°C (lit.\textsuperscript{62} mp 94°C); IR (KBr) 3040, 2900, 2200 (CD), 2140 (CD), 1590, 1490, 1345 and 1160 (SO\textsubscript{2}N), 1080, 770, 750, 690, 590 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 2.4 (br s, 0.4 H), 7.0-7.5 (m, (H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) 143.43, 141.41, 132.66, 129.35, 128.33, 127.92, 127.26, 126.62; mass spectrum, m/e (intensity) 269 (21, M+2), 268 (65, M+1), 267 (330, M), 266 (104), 265 (123), 261 (166), 203 (122), 202 (84), 201 (50), 200 (15), 197 (14).

Crossover Reaction of 170 and 172 with n-Butyllithium. Equimolar amounts of the sulfonamide 170 (0.136 g, 0.522 mmol) and 172 (0.140 g, 0.522 mmol) were dissolved in dry THF (15 mL) under nitrogen in an oven-dried, three-necked, round-bottomed flask equipped with a magnetic stirrer, septum cap and a nitrogen inlet and outlet. A water bath was used to absorb the heat of the reaction. n-Butyllithium (2 equivalents, 1.3 mL of a 1.6 M solution in hexane, 2.1 mmol) was added to the solution via syringe. The solution turned brown immediately. The reaction was monitored by TLC.
(methylene chloride) and after fifteen minutes all of the starting material was gone. The reaction was quenched with water (2 mL) and the THF was removed under reduced pressure. The remaining aqueous mixture was extracted three times with ether (60 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography (silica gel, methylene chloride) to give 36.6% rearranged compound (0.101 g): mp 130°C (lit. 135°C); IR (KBr) 3400 (NH), 3040, 2940, 2895, 2800, 2040 (CD), 1960 (CD), 1600, 1560, 1510, 1460, 1325, 1280 and 1140 (SO₂), 1080, 800, 700, 640, 560, 510 cm⁻¹; ¹H (CDCl₃) δ 2.4 (s, 2.4H), 2.8 (d, 1.6H), 3.17 (br s, 1H), 6.1-7.9 (m, 8H); ¹³C NMR (CDCl₃) δ 147.88, 143.82, 139.17, 135.20, 130.29, 129.61, 126.81, 121.61, 115.85, 111.72, 30.07, 21.53; mass spectrum, m/e (intensity) 269 (12, M+2), 268 (39, M+1), 267 (124, M), 266 (114), 265 (15), 264 (12), 263 (169), 262 (117), 261 (351).
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