Synthesis of the Pyrrolidine Ring System by Radical Cyclization

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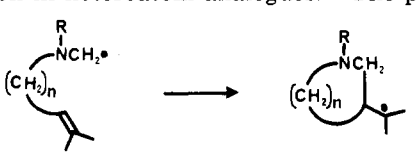
A series of bromo-substituted allyl- and diallyl-substituted sulfonamides have been found to undergo free radical cyclization when treated with tri-*n*-butyltin hydride in the presence of AIBN. The regiochemical course of the cyclization depends on the nature of the substituent groups attached to the π-bond. The stereoelectronic factors governing the cyclization reaction of these *N*-allylsulfonamides are even more stringent than those which occur with the simple 5-hexenyl system. This is probably related to the shorter C–N bond distance which promotes the 5-exo trig cyclization pathway. The present method provides an attractive entry to the preparation of pyrrolidines from easily available *N*-(2-bromoethyl)-*N*-allyl- and *N*-(2-bromopropenyl)-*N*-allylsulfonamides. The method represents a clear-cut example of the use of hetero-substituted radicals in C–C bond-forming processes.

The development of routes for the synthesis of five-membered rings continues to attract attention due largely to the wide variety of natural products containing this structural unit. The pyrrolidine ring represents one of the more extensively studied heterocyclic systems, probably as a consequence of the interesting biological activity exhibited by several polysubstituted pyrrolidines.[1] Particularly useful general approaches to this five-ring heterocycle are the intramolecular ene strategy developed by Oppolzer,[2,3] the electrophilic promoted cyclizations of unsaturated amine derivatives,[4-7] the 1,3-dipolar cycloaddition route,[8-13] the tandem cationic aza-Cope–Mannich cyclization synthesis of Overman,[14] and the transition-metal-catalyzed cyclization of unsaturated amines.[15,16] In connection with our ongoing synthetic program to develop new methods for alkaloid synthesis,[17] we thought it worthwhile to examine a route to pyrrolidines in which a radical cyclization plays a crucial role. Free radical cyclizations are attracting renewed interest from synthetic organic chemists for ring construction as traditional prejudices against free radical intermediates are removed.[18-27] As a result of these studies an appreciation of regiochemical and stereochemical selectivities has been achieved. More recently, such transformations have been incorporated into synthetic approaches to complex target molecules, where the compatibility of a variety of other functional groups to the required reaction conditions proved to be a useful feature.[20-23] The use of hetero-substituted radicals in C–C bond-forming processes, however, has not been widely studied, and only a few examples of heterocyclic synthesis via this method are known.[28-38] Our intention was to study the stereo- and regiochemical aspects of the radical cyclization reaction and to evaluate its potential application for pyrrolidine synthesis. The cyclization of 5-hexen-1-yl radicals to cyclopentylcarbinyl and cyclohexyl radicals is one of the best known radical rearrangements.[39] It is very well documented, and examples abound even in heteroatom analogues. The process is



actually used as a probe for mechanisms,[40-42] being diagnostic in rate[43] and regioselectivity for the radical but not for the ionic species.[44,45]

We began our studies by examining the reaction of several *N*-alkenyl-*N*-(phenylthio)methylamines with tri-*n*-butyltin hydride as a method for generating α-amino free radicals.[29,30] Treatment of benzylamine with 4-bromo-1-

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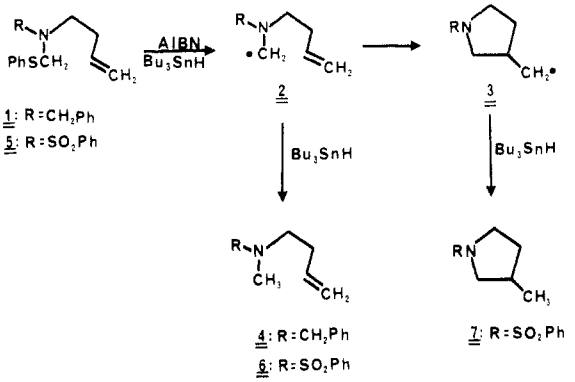
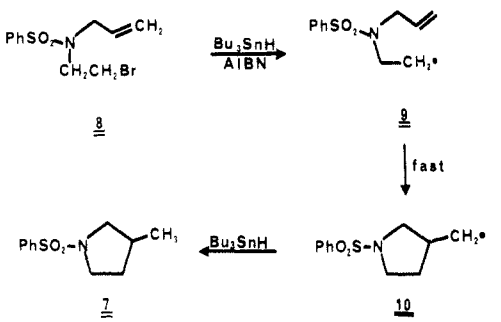
butene gave *N*-benzyl-*N*-(3-butenyl)amine without complications. Reaction of this material with an aqueous formalin solution in the presence of thiophenol produced the desired thio amine **1**. Our initial investigations focused

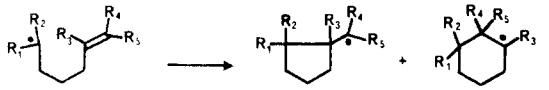


on the generation of radical **2** by treatment of **1** with tri-*n*-butyltin hydride (1.4 equiv) and AIBN (0.04 equiv) in benzene at reflux. The only material isolated (89%) was the noncyclized amine **4**. This result is strikingly different from that encountered with related α-acylamino radicals[29,30] where complete cyclization had occurred. It would seen as though the rate of cyclization is related to the stability of the radical center. Such stabilization has been previously invoked to explain the absence of cyclization products from merostabilized radicals.[46] In an attempt to promote the intramolecular cyclization process, we studied the reaction of the closely related sulfonamide **5**. Placement of an electron-withdrawing sulfonyl group on the nitrogen atom should retard the electronic assistance of the amine group with the radical center thereby enhancing radical cyclization. Our results are consistent with this expectation. The reductive cyclization of sulfonamide **5** afforded pyrrolidine **7** in 36% yield together with some of the noncyclized amine **6**. Although the cyclization of **5** was competitive with reduction, the low yield of **7** imposes a serious limitation to the practicality of the method using *N*-butenyl-substituted sulfonamides.

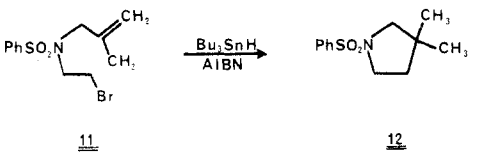
Our attention was next given to the possible intramolecular cyclization of the 2-bromoethyl allyl sulfonamide system **8**. To our delight, when **8** was treated with tri-*n*-butyltin hydride, a 87% yield of **7** was isolated. In this case the intramolecular addition proceeds in a highly regioselective fashion to afford only the product of 1,5-ring closure. A general problem associated with free radical cyclization in media where hydrogen atom transfer reactions are possible is reduction of the radical prior to cyclization. In contrast to the situation that was encountered with sulfonamide **5**, cyclization of radical **9** proceeded quite rapidly since we were unable to detect any reduced product.



Substituent effects on the regiochemistry of cyclization of 5-hexenyl radicals has been studied in some detail by Beckwith,[19] who has summarized his findings as follows.



(1) Substituents at the new radical center (R_4, R_5) show little effect. (2) Substituents on the attacking radical center (R_1, R_2) also show small effects. (3) Substituents on the 2-position of the alkene (R_3) greatly retard the rate of reaction. When a large substituent group is present at C_5 (R_3 = large group), the rate of 1,5-cyclization is lowered to the point where 1,6-cyclization becomes the preferred pathway. Thus, we were quite surprised to find the exclusive formation of the exo cyclized product **12** from the reductive cyclization of sulfonamide **11**. The structure



of **12** was assigned on the basis of its characteristic NMR spectrum, which showed a six-proton singlet at δ 0.88, triplets at 1.48 (2 H, J = 7.0 Hz) and 3.28 (2 H, J = 7.0 Hz), a two-proton singlet at 2.93, and the aromatic hydrogens as a multiplet at 7.4–7.9. None of the 6-endo mode of closure could be detected in the crude reaction mixture by NMR spectroscopy. This result stands in contrast to Hart's observations with the *N*-acyl-2-aza-5-hexenyl radical where both modes of cyclization were encountered.[29] Apparently, the stereoelectronic factors governing the cyclization reaction of **8** and **11** are even more stringent than those which occur with the simple 5-hexenyl system. The length of the C–N bond is less than that of C–C, and the bond angle C–N–C is less than that of C–C–C. The minimum of C_1–C_5 distance in the 3-azahex-5-enyl radical is less than it is in hex-5-enyl, while the C_1–C_6 distance is greater. Therefore, it is not unreasonable to expect the 3-azahex-5-enyl system to undergo ring closure much more rapidly than its hexenyl analogue and to show a greater preference for the exo mode of cyclization. The 5-hexenyl radical cyclizes specifically and irreversibly to the cyclopentylmethyl radical with an absolute rate constant of $k_c \sim 1.0 \times 10^5\ s^{-1}$.[47] Although the rate of cyclization of the 3-azahex-5-enyl radical has not been measured, experiments carried out on closely related systems indicate that replacement of CH_2 with a heteroatom increases the rate of cyclization by an order of magnitude.[48-50] It should be

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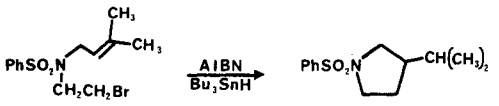
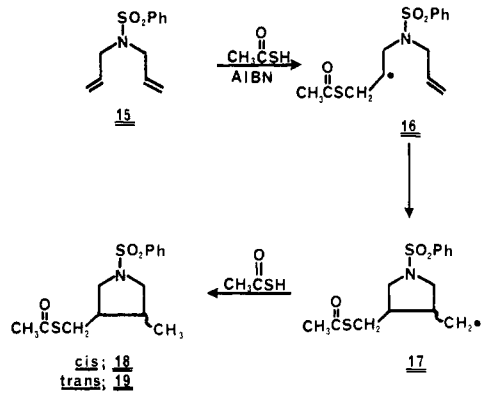
noted that the closely related 3-oxohex-5-enyl radical undergoes exclusive 1,5-ring closure.[50-53] We have found that reductive cyclization of the prenyl-substituted sulfonamide **13** also results in exclusive formation of the expected exo-cyclized product **14**.



13 **14**

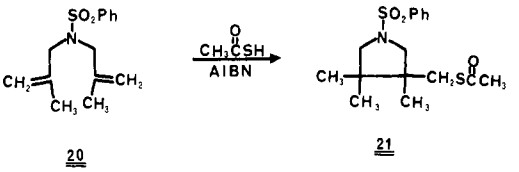
The first report of selective cyclization of a 5-hexenyl free radical generated from a diallylic precursor was made in 1964 by Brace in a study of the free radical chain reaction of 1,6-heptadiene with iodoperfluoropropane.[54] Further work by Brace established the high degree of 1,5-cyclization with diallylamines.[28] We have studied the free radical induced addition of thiolacetic acid to *N,N'*-diallylsulfonamide (**15**) and have found that the initially



15 **16** **17** **cis; 18** **trans; 19**

formed radical also undergoes five-ring closure to give pyrrolidines **18** and **19**. Exo ring cyclization of 5-hexenyl radicals which are monosubstituted at C-1 generally produces mixtures of cis- and trans-disubstituted cyclic products.[19] Thus, the formation of a stereomeric mixture of **18** and **19** from the AIBN induced addition of thiolacetic acid to *N,N'*-diallylsulfonamide is to be expected. The limited experimental data available in the literature suggest that most such reactions conform to the rule[55] that 1,5-ring closures of 1- or 3-substituted systems afford mainly cis-disubstituted products, whereas 2- or 4-substituted systems give mainly trans products. The preferential formation (67%) of the cis isomer **18** derived from sulfonamide **15** is compatible with this general observation.[56,57] The dominance of the cis isomer can be ascribed to the effects of orbital symmetry. The favorable interaction in the transition state for cis cyclization between the hyperconjugatively delocalized semioccupied orbital and the vacant π^* orbital of matching symmetry apparently outweighs the nonbonded repulsion between C-6 and the C-1 substituent.[39]

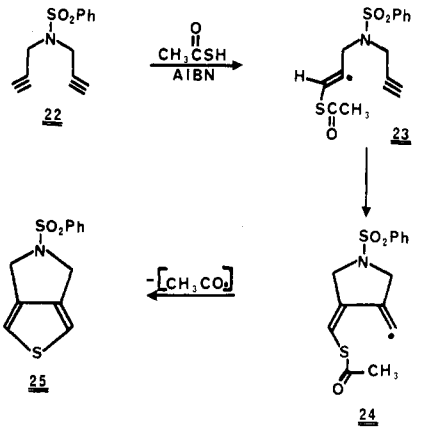
The radical induced cyclization of the closely related *N,N*-bis(2-methyl-2-propenyl)benzenesulfonamide system (**20**) with thiolacetic acid was also studied. Interestingly, the only material isolated corresponded to the 1,5-cyclization product **21** (NMR ($CDCl_3$)) δ 0.73 (s, 3 H), 0.87



20 **21**

(s, 6 H), 2.25 (s, 3 H), 2.72 (s, 2 H), 3.12 (s, 4 H) and 7.5–7.9 (m, 5 H). None of the 6-endo mode of closure could be detected in the crude reaction mixture. This result is similar to that encountered in the reductive cyclization of sulfonamide **11** and reinforces the notion that the shorter C–N bond distance enhances the 5-exo trig cyclization pathway.

We have also examined the free radical induced addition of thiolacetic acid with *N,N*-bis(2-propynyl)benzenesulfonamide (**22**). The major product (55%) isolated from this reaction was a crystalline solid, mp 136–137 °C, whose structure was assigned as 5-(phenylsulfonyl)-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrole (**25**) on the basis of its spectro-



22 **23** **25** **24**

scopic properties (see Experimental Section).[58] Formation of thienopyrrole **25** can be considered to be the result of addition of the thiolacetyl radical onto the triple bond[59] followed by internal 1,5-cyclization. The resulting vinyl radical **24** undergoes a subsequent intramolecular SH_2 reaction[60] on the neighboring sulfur atom to afford the observed product.

During the course of this work, we also examined the cyclization of several *N*-(2-bromopropenyl)-*N*-allylsulfonamides of type **26**. Intramolecular addition of the vinyl radical to the neighboring π-bond at a predictable position would be quite useful since both a process should result in the formation of a nitrogen-containing cycloalkene that could be used for further synthetic manipulations. Earlier work by Stork[61,62] has shown that intramolecular addition of a vinyl radical to a double bond represents a versatile method for the construction of five- and six-ring carbocyclic systems. His results showed that the regiochemical preference in the cyclization of vinyl radicals is qualitatively similar to that observed for the alkyl analogues. The

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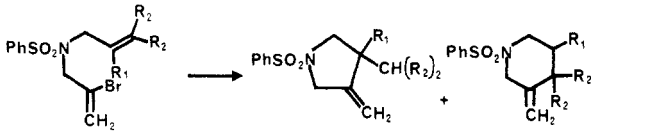
observed five/six-ring preference was suggested to be a consequence of the same geometric factors that have been noted previously in the cyclization of the 5-hexenyl radical.[39]

The vinyl radical cyclizations were all initiated with tributylstannane in the presence of AIBN as the radical initiator. A possible complication with this method is that the relative instability of the vinyl radical[63] might increase the rate of hydrogen abstraction from the stannane and result in simple replacement of the halogen by hydrogen, without cyclization. This proved not to be the case, and the cyclization reaction proceeded quite smoothly. We found that the reductive cyclization of **26** gives a 3:1 ratio of exo and endo cyclization products, respectively, comparable to the ratio observed by Stork in the closely related carbocyclic system.[62]

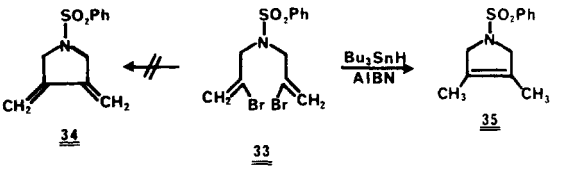
In order to delineate the effect of olefin substitution on the regiochemical course of the reaction, we studied the cyclization of sulfonamides **29** and **31** and found the reactions to proceed with total regioselectivity. With these



26: $R_1 = R_2 = H$ **27**: $R_1 = R_2 = H$ **28**: $R_1 = R_2 = H$
29: $R_1 = H$; $R_2 = CH_3$ **30**: $R_1 = H$; $R_2 = CH_3$ **32**: $R_1 = CH_3$; $R_2 = H$
31: $R_1 = CH_3$; $R_2 = H$

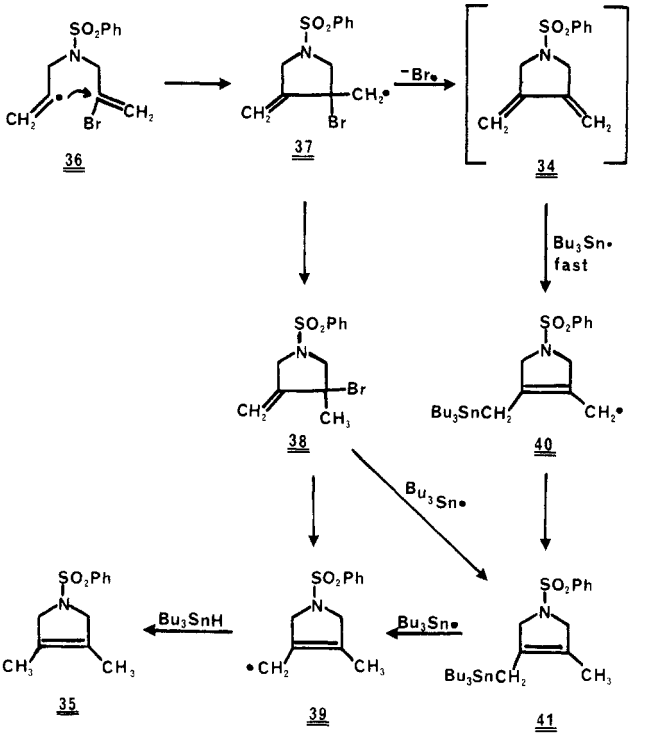
systems, favorable stereoelectronic factors promote the observed selectivity. Thus, replacement of hydrogen with a methyl group for sulfonamide **31** ($R_1 = CH_3$) has a profound effect on the regioselectivity of ring closure leading only to six-ring cyclization. By analogy to the situation with the simple 5-hexenyl system, introduction of a substituent in the 5-position apparently results in a severe nonbonded interaction in the transition state leading toward exo ring closure. The high regioselectivity encountered with sulfonamides **29** and **31** supports the view that these cyclizations require the approach of the radical within the plane of the π-orbital and along an axis extending approximately vertically above one of the terminal atoms of the double bond. The basis for this model rests on the suggestion[64] that the primary interaction involves overlap of the half-filled orbital of the radical with one lobe of the vacant π^* orbital, a view supported by an MO treatment of the addition of a radical to ethylene.[65] It is important to note, however, the marked difference in the mode of cyclization of the saturated (11-exo closure) and unsaturated (31-endo closure) sulfonamides. It would seem that subtle steric and electronic effects, which we do not fully understand, are responsible for the regiochemical outcome of the vinyl cyclization reactions.

As a further continuation of our work in this area, we have also studied the reaction of *N,N*-bis(2-bromo-2-propenyl)benzenesulfonamide (**33**) with tri-*n*-butyltin hydride with the hope that we could induce ring closure to give diene **34**. The ready availability of this diene might allow for the synthesis of a series of novel isoindole derivatives via the Diels–Alder reaction. We found, however, that treatment of **33** with tri-*n*-butyltin hydride and AIBN in refluxing benzene afforded the dimethyl-substituted 3-pyrroline **35** as the only isolable product. The structure



of this material was established on the basis of its analytical and spectroscopic properties (see Experimental Section). All attempts to detect the presence of diene **34** in the crude reaction mixture failed.

The conversion of **33** to **35** is an interesting reaction which merits some comment. A number of pathways seem possible. One path involves cyclization of the initially formed vinyl radical **36** to give intermediate **37**. This



species then abstracts a hydrogen atom from tin hydride to produce allyl bromide **38**. Further reaction of this species with another tri-*n*-butyltin radical affords **39**, which is ultimately converted to the observed product. Alternatively, **37** can undergo loss of a bromine atom to give **34** as a transient species which rapidly reacts with a stannyl radical to produce radical **40**. Hydrogen abstraction followed by reaction of **41** with an additional tin radical gives **39** and then **35**. Another mechanistic scenario is that **38** reacts with a tri-*n*-butyltin radical to give **41**. At the current time the available data do not distinguish between these various possibilities.

In summary, the free radical cyclization of several bromo allyl- and diallylsulfonamides provides ready access to the pyrrolidine ring system. Although the regiochemical course of the cyclization depends on the nature of the substituent groups attached to the π-bond, 1,5-cyclization is the generally preferred path. This method is currently being used in our laboratory to synthesize a number of alkaloids possessing the pyrrolidine ring.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 283 infrared spectrometer. Proton NMR spectra were obtained on Varian EM-390 and Nicolet FT-360 spectrometers. ^{13}C NMR spectra were recorded on an IBM 200-MHz spectrometer. Microanalyses were performed

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at Atlantic Microlabs, Atlanta, GA. Mass spectra were determined with a Finnegan 4000 mass spectrometer at an ionizing voltage of 70 eV.

Preparation of *N*-(3-Butenyl)-*N*-((phenylthio)methyl)-benzenemethanamine (1). To a sample containing 35.7 g of benzylamine at 90 °C was added dropwise 15 g of 4-bromo-1-butene over a period of 30 min. After the addition was complete, the mixture was heated at 90 °C for an additional 3 h. The reaction mixture was cooled and then poured into a cold 10% sodium hydroxide solution. The aqueous mixture was extracted with ether, and the ether solution was washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was fractionally distilled through a Vigereux column under reduced pressure to give 9.59 g (53%) of *N*-benzyl-*N*-(3-butenyl)amine, bp 105–107 °C (7.5 mm): NMR (CCl_4, 90 MHz) δ 1.02 (br s, 1 H), 2.05–2.28 (m, 2 H), 2.53–2.69 (m, 2 H), 3.70 (s, 2 H), 4.90–5.13 (m, 2 H), 5.53–5.95 (m, 1 H), 7.19 (s, 5 H); IR (neat) 3320, 3075, 3040, 2920, 2820, 1640, 1500, 1450, 1120, 995, 920, 735 and 700 cm^{-1}.

To an ice-cooled sample of 3.22 g of the above amine was added 2.05 mL of thiophenol, followed by 1.62 g of a 37% aqueous formalin solution. The mixture was allowed to warm to room temperature and was then heated at 80 °C for 3 h. The mixture was cooled and extracted with ether, and the organic layer was washed with a 10% sodium hydroxide solution followed by a saturated sodium chloride solution. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography using a 1% ethyl acetate–hexane mixture as the eluent. The major fraction isolated contained 4.87 g (86%) of *N*-(3-butenyl)-*N*-((phenylthio)methyl)benzenemethanamine (1) as a colorless oil: IR (neat) 3080, 3050, 2960, 2850, 1650, 1590, 1490, 1465, 1450, 1380, 1270, 1175, 1100, 1040, 925, 750, and 705 cm^{-1}; NMR (CCl_4, 90 MHz) δ 2.0–2.25 (m, 2 H), 2.68 (t, 2 H, J = 7.5 Hz), 3.68 (s, 2 H), 4.38 (s, 2 H), 4.83–5.09 (m, 2 H), 5.68 (ddt, 1 H, J = 17.4, 9.45, and 6.3 Hz), 7.05–7.50 (m, 10 H); UV (95% ethanol) 240 nm (ϵ 6980); ms, m/e 283 (M^+), 174 and 91 (base). Anal. Calcd for $C_{18}H_{21}NS$: C, 76.28; H, 7.47; N, 4.94; S, 11.31. Found: C, 76.23; H, 7.49; N, 4.87; S, 11.36.

Reaction of *N*-(3-Butenyl)-*N*-((phenylthio)methyl)-benzenemethanamine (1) with Tri-*n*-butyltin Hydride. A solution containing 1.0 g of 1, 1.03 g of tri-*n*-butyltin hydride, and a catalytic amount of AIBN in 100 mL of anhydrous benzene was heated at reflux for 6 h under a nitrogen atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to silica gel flash chromatography using a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 0.36 g (59%) of *N*-(3-butenyl)-*N*-methylbenzenemethanamine (4): IR (neat) 3080, 3045, 3000, 2960, 2855, 2800, 1645, 1500, 1460, 1375, 1030, 920, 740, and 700 cm^{-1}; NMR (CCl_4, 90 MHz) δ 2.13 (s, 3 H), 2.17–2.50 (m, 2 H), 3.42 (s, 2 H), 4.87–5.13 (m, 2 H), 5.77 (ddt, 1 H, J = 17.4, 10.2, and 6.60 Hz), 7.19 (s, 5 H); ms, m/e 175 (M^+), 174, 134, 92, 91 (base), and 65. Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.27; H, 9.80; N, 7.90.

The structure of 4 was confirmed by an independent synthesis. A mixture containing 1.35 g of 4-bromo-2-butene and 2.42 g of *N*-benzylmethylamine was heated at 85 °C for 2 h. After standard workup, the residue was chromatographed on a silica gel column using a 10% ethyl acetate–hexane mixture as the eluent to give 1.39 g (79%) of *N*-(3-butenyl)-*N*-methylbenzenemethanamine (4) as a colorless oil which was identical in all respects with the sample obtained from the tin hydride reduction of 1.

Preparation and Reaction of *N*-(3-Butenyl)-*N*-((phenylthio)methyl)benzenesulfonamide (5) with Tri-*n*-butyltin Hydride. A solution containing 1.0 g of *N*-(3-butenyl)-*N*-benzenesulfonamide was added dropwise to a suspension containing 0.24 g of sodium hydride in 25 mL of DMF at room temperature under a nitrogen atmosphere. After hydrogen evolution had ceased, a solution containing 0.75 g of chloromethyl phenyl sulfide in 2 mL of anhydrous DMF was added. The reaction mixture was stirred at room temperature for 4.5 h. After standard workup, the oily residue was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 1.10 g (70%) of *N*-(3-butenyl)-*N*-(phenylthio)methyl)benzenesulfonamide (5) as a colorless oil: IR (neat) 3070, 2940, 1650, 1590, 1485, 1450, 1345, 1165, 1090, 1025, 1000, 965, 925, 745, and 690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.05–2.25 (m, 2 H), 3.23–3.40 (m, 2 H), 4.82–5.08 (m, 4 H), 5.38–5.82 (m, 1 H), 7.17–7.85 (m, 10 H); UV (95% ethanol) 248 nm (ϵ 7640); ms, m/e 292, 224, 170, 141, and 77. Anal. Calcd for $C_{17}H_{19}NO_2S_2$: C, 61.23; H, 5.74; N, 4.20; S, 19.23. Found: C, 61.31; H, 5.78; N, 4.19; S, 19.23.

A mixture containing 0.5 g of 5, 0.44 g of tri-*n*-butyltin hydride, and 0.1 g of AIBN in 100 mL of anhydrous benzene was heated at reflux under a nitrogen atmosphere. After heating for 8 h, the reaction mixture was briefly cooled, and another 0.1 g of AIBN was added to the solution. The reaction mixture was heated at reflux for an additional 10 h, and then the reaction mixture was cooled. The solvent was removed under reducted pressure, and the residue was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent. The first fraction contained 0.31 g of a tin containing substrate. The second fraction contained 0.20 g (40%) of unreacted starting material. The third fraction contained 15 mg (39%) of a clear oil whose structure was assigned as *N*-3-butenyl-*N*-methylbenzenesulfonamide on the basis of its NMR spectrum which showed peaks at δ 2.13 (s, 3 H), 2.05–2.28 (m, 2 H), 3.23–3.40 (m, 2 H), 4.87–5.13 (m, 2 H), 5.48–5.80 (m, 1 H), and 7.1–7.8 (m, 5 H). The fourth fraction contained 165 mg (36%) of the sulfonamide *N*-(phenylsulfonyl)-3-methylpyrrolidine (7) as a colorless oil: IR (neat) 3080, 2980, 2790, 1490, 1450, 1345, 1165, 1100, 1050, 760, 720, 695, and 605 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.91 (d, 3 H, J = 6.48 Hz), 1.31–1.41 (m, 1 H), 1.87–1.96 (m, 1 H), 2.05–2.20 (m, 1 H), 2.77 (dd, 1 H, J = 9.72 and 7.74 Hz), 3.24 (ddd, 1 H, J = 9.72, 7.92, and 7.20 Hz), 3.36 (ddd, 1 H, J = 9.72, 8.1, and 4.32 Hz), 3.44 (dd, 1 H, J = 9.72 and 7.20 Hz), 7.51–7.85 (m, 5 H); UV (95% ethanol) 226 nm (ϵ 7370); ms, m/e 225 (M^+), 224, 141, 84 (base), and 77. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22; S, 14.23. Found: C, 58.73; H, 6.75; N, 6.18; S, 14.18.

Preparation and Reaction of *N*-(2-Bromoethyl)-*N*-(2-propenyl)benzenesulfonamide (8) with Tri-*n*-butyltin Hydride. A mixture containing 2.42 g of allyl bromide, 3.14 g of benzenesulfonamide, and 2.76 g of potassium carbonate in 60 mL of anhydrous acetone was heated at reflux for 36 h. After standard workup, the residue was subjected to silica gel chromatography with a 20% ethyl acetate–hexane mixture as the eluent. The first fraction isolated from the plate contained 1.06 g (22%) of *N*,*N*-bis(2-propenyl)benzenesulfonamide (15) as a colorless oil: IR (neat) 3095, 3020, 3000, 2930, 1650, 1450, 1425, 1350, 1160, 1090, 995, 930, 780, 755, and 695 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.82 (br d, 4 H, J = 6.0 Hz), 5.0–5.30 (m, 4 H), 5.43–5.83 (m, 2 H), 7.40–7.63 (m, 3 H), 7.73–7.93 (m, 2 H). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 60.65; H, 6.25; N, 5.89.

The second fraction contained 1.17 g (30%) of *N*-(2-propenyl)benzenesulfonamide as a colorless oil: IR (neat) 3620, 3290, 3080, 2860, 1650, 1450, 1325, 1160, 1090, 1070, 930, 845, 760, 720, and 690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.46 (m, 2 H), 4.97–5.33 (m, 3 H), 5.70 (ddt, 1 H, J = 16.8, 9.60, and 5.40 Hz), 7.35–7.63 (m, 3 H), 7.77–8.10 (m, 2 H).

To a solution containing 0.45 g of the above compound in 25 mL of anhydrous DMF under a nitrogen atmosphere was added 0.82 g of anhydrous cesium carbonate. After stirring for 20 min, 0.58 mL of 1,2-dibromoethane was added. The mixture was allowed to stir at room temperature for 20 h. After standard workup, the residue was subjected to silica gel chromatography with a 20% ethyl acetate–hexane mixture as the eluent. The first fraction contained 0.27 g (39%) of a colorless oil whose structure was assigned as *N*-(2-bromoethyl)-*N*-(2-propenyl)benzenesulfonamide (8) on the basis of its spectroscopic properties: IR (neat) 3040, 2950, 2940, 1645, 1590, 1480, 1450, 1340, 1285, 1210, 1160, 1090, 1050, 920, 790, 750, and 690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.46 (s, 4 H), 3.85 (d, 2 H, J = 6.0 Hz), 5.07–5.33 (m, 2 H), 5.70 (ddt, 1 H, J = 16.8, 9.0, and 6.0 Hz), 7.47–7.67 (m, 3 H), 7.77–7.93 (m, 2 H); ms, m/e 305 (M^+), 303, 210 (base), 141, and 77. Anal. Calcd for $C_{11}H_{14}BrNO_2S$: C, 43.43; H, 4.64; N, 4.61; Br, 26.27. Found: C, 43.52; H, 4.69; N, 4.56; Br, 26.22.

A solution containing 0.22 g of 8, 0.21 g of tri-*n*-butyltin hydride, and 50 mg of AIBN in 25 mL of anhydrous benzene was heated at reflux under a nitrogen atmosphere for 9.5 h. After cooling to room temperature, the solvent was removed under reduced

pressure, and the residue was subjected to silica gel chromatography with a 20% ethyl acetate–hexane mixture as the eluent to give 125 mg (77%) of *N*-(phenylsulfonyl)-3-methylpyrrolidine (**7**) which was identical with a sample of **7** prepared from the reaction of benzenesulfonamide **5** with tri-*n*-butyltin hydride.

Preparation and Reaction of *N*-(2-Bromoethyl)-*N*-(2-methyl-2-propenyl)benzenesulfonamide (11) with Tri-*n*-butyltin Hydride. A mixture containing 9.0 g of 3-chloro-2-methyl-1-propene, 16 g of benzenesulfonamide, and 13 g of potassium carbonate in 150 mL of acetone was heated at reflux for 36 h. The mixture was diluted with ether and washed with water. The ether layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was taken up in 30 mL of chloroform and 30 mL of hexane, and the resulting benzenesulfonamide was separated by crystallization. The residue was chromatographed on a silica gel column with a 10% ethyl acetate–hexane mixture as the eluent. The first fraction contained 5.5 g of *N,N*-bis(2-methyl-2-propenyl)benzenesulfonamide (**20**) as a colorless oil: IR (neat) 3080, 2985, 2920, 1660, 1590, 1450, 1350, 1160, 1100, 1020, 920, 800, 750, and 690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.60 (s, 6 H), 3.73 (br s, 4 H), 4.76 (s, 2 H), 4.83 (2 H), and 7.33–7.90 (m, 2 H). The second fraction contained 4.5 g (20%) of *N*-(2-methyl-2-propenyl)benzenesulfonamide as a colorless oil: IR (neat) 3300, 3080, 3000, 2930, 2830, 1660, 1590, 1450, 1330, 1160, 1095, 1070, 900, 850, 760, 740, and 690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.63 (s, 3 H), 3.62 (d, 2 H, J = 7.0 Hz), 4.75 (s, 1 H), 4.82 (s, 1 H), 5.20 (t, 1 H, J = 7.0 Hz) and 7.13–7.93 (m, 5 H). This material was used in the next step without further purification.

To a solution containing 0.63 g of the latter compound in 30 mL of anhydrous dimethylformamide under a nitrogen atmosphere was added 1.0 g of cesium carbonate. After stirring for 20 min, 1.70 g of 1,2-dibromoethane was added. The mixture was allowed to stir at room temperature for an additional 20 h. After standard workup, the residue was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 0.39 g (42%) of a colorless oil whose structure was assigned as *N*-(2-bromoethyl)-*N*-(2-methyl-2-propenyl)benzenesulfonamide (**11**) on the basis of its spectral properties: IR (neat) 3080, 2985, 1660, 1590, 1450, 1340, 1160, 1090, 1015, 920, 855, 790, 760, and 695 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.70 (s, 3 H), 3.43 (br s, 4 H), 3.75 (s, 2 H), 4.90 (br s, 2 H), 7.43–7.87 (m, 5 H). Anal. Calcd for $C_{12}H_{16}NO_2SBr$: C, 45.29; H, 5.08; N, 4.40. Found: C, 45.32; H, 5.11; N, 4.37.

A solution containing 1.12 g of **11**, 1.1 g of tri-*n*-butyltin hydride, and 0.3 g of AIBN in 100 mL of benzene was heated at reflux for 10 h. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent to give 0.69 g (85%) of a colorless oil whose structure was assigned as *N*-(phenylsulfonyl)-3,3-dimethylpyrrolidine (**12**): IR (neat) 3060, 2960, 2870, 1590, 1465, 1445, 1340, 1160, 1095, 1050, 1000, 930, 800, 750, 730, and 690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.88 (s, 6 H), 1.48 (t, 2 H, J = 7.0 Hz), 2.93 (s, 2 H), 3.28 (t, 2 H, J = 7.0 Hz) and 7.37–7.87 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.69 (q), 33.34 (s), 38.85 (t), 46.79 (t), 59.98 (t), 127.06 (d), 128.75 (d), 132.35 (d), 136.79 (s). Anal. Calcd for $C_{12}H_{17}NSO_2$: C, 60.21; H, 7.17; N, 5.85. Found: C, 60.30; H, 7.21; N, 5.81.

Preparation and Reaction of *N*-(2-Bromoethyl)-*N*-(3-methyl-2-butenyl)benzenesulfonamide (13) with Tri-*n*-butyltin Hydride. A mixture containing 7.3 g of benzenesulfonamide, 8.0 g of 3-bromo-2-methyl-2-butene, and 7.0 g of potassium carbonate in 100 mL of acetone was heated at reflux for 36 h. The mixture was diluted with ether and extracted with water. The ethereal solution was dried over magnesium sulfate, and the solvent was removed under reduced pressure. The unreacted benzenesulfonamide was removed by filtration from 20 mL of a 1:1 chloroform–hexane mixture. The residue was chromatographed on a silica gel column with 20% ethyl acetate–hexane as the eluent. The first fraction isolated contained 1.2 g (9%) of *N,N*-bis(3-methyl-2-butenyl)benzenesulfonamide as a colorless oil: IR (neat) 3080, 2980, 2940, 1750, 1680, 1450, 1370, 1350, 1240, 1170, 1100, 1080, 1030, 920, 850, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.57 (s, 6 H), 1.63 (s, 6 H), 3.76 (d, 4 H, J = 7.0 Hz), 5.01 (t, 2 H, J = 7.0 Hz), and 7.35–7.87 (m, 5 H). The second fraction from the column contained 7.5 g (65%) of *N*-(3-methyl-2-butenyl)benzenesulfonamide: IR (neat) 3290, 3080, 2980, 2930, 2860, 1680, 1590, 1450, 1330, 1160, 1095, 1060, 830, 760, 730, and 695 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.52 (s, 3 H), 1.58 (s, 3 H), 3.53 (t, 2 H, J = 7.0 Hz), 4.9–5.2 (m, 2 H), and 7.37–7.95 (m, 5 H). This material was used in the next step without further purification.

To a solution containing 0.9 g of the latter compound in 30 mL of anhydrous DMF was added 1.6 g of cesium carbonate. After stirring for 20 min, 2.26 g of 1,2-dibromoethane was added, and the mixture was allowed to stir at 25 °C for an additional 20 h. After standard workup, the residue was subjected to silica gel chromatography with a 20% ethyl acetate–hexane mixture as the eluent. The major fraction isolated from the plate contained 0.58 g (44%) of a colorless oil whose structure was assigned as *N*-(2-bromoethyl)-*N*-(3-methyl-2-butenyl)benzenesulfonamide (**13**) on the basis of its spectral properties: IR (neat) 3080, 2980, 2930, 2870, 1680, 1590, 1450, 1340, 1150, 1090, 935, 860, 770, and 695 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.65 (s, 3 H), 1.68 (s, 3 H), 3.40 (s, 2 H), 3.76 (d, 2 H, J = 7.0 Hz), 5.02 (t, 1 H, J = 7.0 Hz), 7.37–7.83 (m, 5 H). Anal. Calcd for $C_{13}H_{18}NO_2SBr$: C, 46.99; H, 5.47; N, 4.22. Found: C, 47.08; H, 5.50; N, 4.18.

A solution containing 1.08 g of **13**, 1.0 g of tri-*n*-butyltin hydride, and 0.3 g of AIBN in 100 mL of benzene was heated at reflux for 10 h. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent to give 0.84 g (84%) of the sulfonamide *N*-(phenylsulfonyl)-3-isopropylpyrrolidine (**14**) as a colorless oil: IR (neat) 3075, 2960, 2870, 1670, 1650, 1350, 1170, 1100, and 1030 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.85 (d, 6 H, J = 6.8 Hz), 1.30–1.45 (m, 2 H, 1.60–1.77 (m, 1 H), 1.92 (ttd, 1 H, J = 8.3, 5.4, and 3.5 Hz), 2.81 (t, 1 H, J = 9.7 Hz), 3.18 (ddd, 1 H, J = 9.9, 9.7, and 6.8 Hz), 3.44 (ddd, J = 9.7, 8.3, and 2.2), 3.48 (dd, J = 9.7 and 7.6 Hz), and 7.45–7.88 (m, 5 H); ^{1C} NMR ($CDCl_3$, 50 MHz) δ 20.62 (q), 20.99 (q), 29.70 (t), 31.39 (d), 46.21 (d), 47.93 (t), 51.79 (t), 127.22 (d), 128.80 (d), 132.33 (d), and 136.60 (s). Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.61; H, 7.57; N, 5.53. Found: C, 61.72; H, 7.58; N, 5.49.

Reaction of *N,N*-Bis(2-propenyl)benzenesulfonamide (15) with Thiolacetic Acid in the Presence of AIBN. A mixture containing 0.92 g of **15**, 0.30 mL of thiolacetic acid, and a small amount of AIBN in 100 mL of anhydrous benzene was heated at reflux under a nitrogen atmosphere for 8 h. The solution was cooled, and the solvent was removed under reduced pressure. The resulting residue was subjected to silica gel chromatography with a 20% ethyl acetate–hexane mixture was the eluent. The major fraction isolated from the plate contained 1.22 g (100%) of a colorless oil whose structure was assigned as a 2:1 diastereomeric mixture of *cis*- and *trans*-*N*-(phenylsulfonyl)-3-methyl-4-((acetylthio)methyl)pyrrolidine (**18** and **19**): IR (neat) 3080, 2980, 2900, 1695, 1490, 1450, 1350, 1170, 1100, 1050, 965, 765, 725, and 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ cis isomer 0.81 (d, J = 6.84 Hz) and trans isomer 0.96 (d, J = 6.48 Hz) (3 H), 1.77–1.89 (m, 1 H), 2.18–2.29 (m, 1 H), 2.31 and 2.32 (s, 3 H), 2.50 and 2.54 (d, J = 9 Hz), 2.62 and 2.66 (d, J = 7.92 Hz), (1 H), 2.80–3.10 (m, 3 H), 3.38–3.55 (m, 2 H), 7.52–7.85 (m, 5 H); UV (95% ethanol) 228 nm (ϵ 12 800); MS, m/e 270, 237, 210, 172, 141, 96, and 77 (base). Anal. Calcd for $C_{14}H_{19}NO_3S_2$: C, 53.65; H, 6.11; N, 4.47; S, 20.46. Found: C, 53.69; H, 61.16; N, 4.43; S, 20.54.

Reaction of *N,N*-Bis(2-methyl-2-propenyl)benzenesulfonamide (20) with Thiolacetic Acid in the Presence of AIBN. A mixture containing 1.06 g of **20**, 0.4 mL of thiolacetic acid, and a small amount of AIBN in 100 mL of benzene was heated at reflux for 8 h. The cooled solution was concentrated under reduced pressure, and the resulting residue was subjected to silica gel chromatography with a 5% ethyl acetate–hexane mixture as the eluent. The major fraction contained 864 mg (64%) of *N*-(phenylsulfonyl)-3,3-dimethyl-4-((acetylthio)methyl)-pyrrolidine (**21**) as a colorless oil: IR (neat) 2980, 2890, 1700, 1450, 1350, 1160, 1100, 1060, 960, 820, 760, 730, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.73 (s, 3 H), 0.87 (s, 6 H), 2.25 (s, 3 H), 2.72 (s, 2 H), 3.12 (s, 4 H), and 7.5–7.9 (m, 5 H). Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 56.27; H, 6.80; N, 4.10. Found: C, 56.27; H, 6.84; N, 4.08.

Preparation of *N,N*-Bis(2-propynyl)benzenesulfonamide (22). A mixture containing 8.0 g of propargyl chloride, 3.73 g of benzenesulfonamide, and 7.0 g of potassium carbonate in 150 mL of anhydrous acetone was heated at reflux for 36 h. The mixture

was cooled, diluted with ether, and washed with water and a saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was treated with 30 mL of chloroform, and the resulting solid was separated and identified as unreacted benzenesulfonamide. The residue was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 1.6 g (88%) of *N*,*N*-bis(2-propynyl)benzenesulfonamide (**22**) as a crystalline solid, mp 85–86 °C: IR (KBr) 3260, 3070, 2120, 1590, 1490, 1450, 1340, 1130, 960, 770, and 750 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.10 (t, 2 H, 3.0 Hz), 4.18 (d, 4 H, J = 3.0 Hz) and 7.4–7.8 (m, 5 H). Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.77; H, 4.76; N, 6.01. Found: C, 61.72; H, 4.61; N, 5.87.

Reaction of *N*,*N*-Bis(2-propynyl)benzenesulfonamide (22) with Thiolacetic Acid in the Presence of AIBN. A mixture containing 885 mg of **22**, 380 mg of thiolacetic acid, and 0.3 mmol of AIBN in 100 mL of benzene was heated at reflux for 40 h. At the end of 15 and 30 h, an additional quantity of AIBN was added. The cooled solution was washed with a potassium carbonate solution and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 580 mg (55%) of a crystalline solid, mp 136–137 °C, whose structure was assigned as 5-(phenylsulfonyl)-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrole (**25**) on the basis of its characteristic spectral data: IR (KBr) 3100, 1445, 1335, 1315, 1150, 1100, 1050, 800, 720, 690, 620, 570, and 540 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 4.42 (s, 4 H), 6.85 (s, 2 H), 7.45–7.65 (m, 3 H) and 7.79–7.98 (m, 2 H). Anal. Calcd for $C_{12}H_{11}NO_2S_2$: C, 54.31; H, 4.19; N, 5.28. Found: C, 54.38; H, 4.20; N, 5.24.

Preparation and Reaction of *N*-(2-Bromo-2-propenyl)-*N*-(2-propenyl)benzenesulfonamide (26) with Tri-*n*-butyltin Hydride. To a solution containing 0.76 g of *N*-(2-propenyl)-benzenesulfonamide in 25 mL of anhydrous DMF at room temperature was added 1.51 g of anhydrous cesium fluoride under a nitrogen atmosphere. After stirring for 15 min, 0.48 mL of 2,3-dibromopropene was added. The mixture was stirred for an additional 36 h. After standard workup, the oily residue was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 0.80 g (76%) of *N*-(2-bromo-2-propenyl)-*N*-(2-propenyl)-benzenesulfonamide (**26**) as a colorless oil: IR (neat) 3075, 2980, 1630, 1486, 1450, 1350, 1160, 1090, 905, 785, 755, 720, and 690 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.87 (d, 2 H, J = 3.6 Hz), 4.05 (s, 3 H), 5.12–5.18 (m, 2 H), 5.60–5.62 (m, 2 H), 5.83–5.85 (m, 1 H); MS, m/e 317 (M^+), 315, 236 (base), 141, 96, and 77. Anal. Calcd for $C_{12}H_{14}BrNO_2S$: C, 45.58; H, 4.46; N, 4.43; Br, 25.27. Found: C, 45.40; H, 4.52; N, 4.39; Br, 25.18.

A mixture containing 730 mg of **26**, 670 mg of tri-*n*-butyltin hydride, and a catalytic amount of ABIN in 50 mL of anhydrous benzene was heated at reflux under a nitrogen atmosphere for 8 h. The solvent was removed under reduced pressure, and the residue was subjected to silica gel flash chromatography. The major fraction contained 490 mg of a mixture of two products. Fractional recrystallization of the mixture gave 300 mg of *N*-(phenylsulfonyl)-2-methylenepiperidine (**28**), mp 94–95 °C, whose structure was assigned on the basis of its spectroscopic properties: IR ($CHCl_3$) 2950, 2840, 1660, 1605, 1440, 1350, 1165, 1010, 980, 920, and 620 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.66–1.72 (m, 2 H), 2.11 (t, 2 H, J = 6.12 Hz), 3.10 (t, 2 H, J = 5.40 Hz), 3.54 (s, 2 H), 4.83 (s, 1 H), 4.90 (s, 1 H), 7.52–7.80 (m, 5 H); MS, m/e 237 (M^+), 141, 96, and 69 (base). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51. Found: C, 60.82; H, 6.41; N, 5.86; S, 13.48.

The other component (150 mg) was assigned as *N*-(phenylsulfonyl)-3-methyl-4-methylenepyrrolidine (**27**) on the basis of its 360-MHz NMR spectrum: δ 1.04 (d, 3 H, J = 6.48 Hz), 2.63–2.74 (m, 2 H), 3.60 (dd, 1 H, J = 8.10 and 6.48 Hz), 2.63–2.74 (m, 2 H), 3.60 (dd, 1 H, J = 8.10 and 6.48 Hz), 3.76 (ddd, 1 H, J = 14.04, 3.60, and 1.80 Hz), 3.97 (br d, 1 H, J = 14.04 Hz), 4.85–4.92 (m, 2 H), 7.52–7.85 (m, 5 H); IR ($CHCl_3$) 2940, 2820, 1655, 1605, 1430, 1340, 1160, 1010, 970, 920, and 625 cm^{-1}; MS, m/e 237 (M^+), 141, 96, and 69 (base). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51. Found: C, 60.61; H, 6.20; N, 5.73; S, 13.28.

Preparation and Reaction of *N*-(2-Bromo-2-propenyl)-*N*-(3-methyl-2-butenyl)benzenesulfonamide (29). To a solution containing 1.0 g of *N*-(3-methyl-2-butenyl)benzenesulfonamide in 30 mL of DMF at 25 °C was added 1.8 g of cesium carbonate. After stirring for 15 min, 2.0 g of 2,3-dibromopropene was added, and the mixture was stirred for an additional 24 h and worked up in the usual fashion. The residue was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent. The major fraction isolated from the column contained 1.14 g (83%) of *N*-(2-bromo-2-propenyl)-*N*-(3-methyl-2-butenyl)benzenesulfonamide (**29**) as a colorless oil: IR (neat) 3070, 2980, 2930, 1675, 1630, 1445, 1350, 1160, 1090, 1070, 1020, 900, 850, 790, 780, and 690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.58 (s, 3 H), 1.60 (s, 3 H), 3.78 (d, 2 H, J = 9.0 Hz), 3.95 (s, 2 H), 4.88 (t, 1 H, J = 9.0 Hz), 5.33 (br s, 1 H), 5.80 (br s, 1 H), and 7.37–7.83 (m, 5 H). Anal. Calcd for $C_{14}H_{18}NO_2SBr$: C, 48.84; H, 5.28; N, 4.07. Found: C, 48.90; H, 5.30; N, 4.03.

A mixture containing 1.0 g of **29**, 1.0 g of tri-*n*-butyltin hydride, and 0.3 g of AIBN in 100 mL of benzene was heated at reflux for 10 h. Removal of the solvent under reduced pressure left an oily residue which was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 0.52 g (67%) of *N*-(phenylsulfonyl)-4-isopropyl-3-methylenepyrrolidine (**30**) as a colorless oil: IR (neat) 3060, 2950, 2860, 1665, 1590, 1480, 1460, 1440, 1350, 1170, 1090, 1070, 1000, 900, and 830 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.80 (d, 3 H, J = 6.5 Hz), 0.89 (d, 3 H, J = 6.5 Hz), 1.68–1.77 (m, 1 H), 2.41–2.50 (m, 1 H), 3.18 (dd, 1 H, J = 10.0 and 4.9 Hz), 3.30 (dd, 1 H, J = 10.0 and 7.6 Hz), 3.79 (br s, 2 H), 4.88 (br s, 1 H), 4.97 (br s, 1 H), and 7.52–7.85 (m, 5 H). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.35; H, 7.23; N, 5.28. Found: C, 63.28; H, 7.27; N, 5.28.

Preparation and Reaction of *N*-(2-Bromo-2-propenyl)-*N*-(2-methyl-2-propenyl)benzenesulfonamide (31) with Tri-*n*-butyltin Hydride. To a solution containing 1.0 g of *N*-(2-methyl-2-propenyl)benzenesulfonamide in 30 mL of DMF at 25 °C was added 2.0 g of cesium carbonate. After stirring for 15 min, 2.0 g of 2,3-dibromopropene was added. The mixture was stirred for 24 h and was worked up in the usual fashion. The residue was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent. The major fraction isolated from the plate contained 1.56 g (94%) of *N*-(2-bromo-2-propenyl)-*N*-(2-methyl-2-propenyl)benzenesulfonamide (**31**) as a colorless oil: IR (neat) 3080, 2980, 2920, 1630, 1590, 1445, 1340, 1150, 1090, 1020, 900, 790, 750, and 690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.63 (s, 3 H), 3.80 (s, 2 H), 4.00 (s, 2 H), 4.80 (s, 1 H), 4.88 (s, 1 H), 5.48 (br s, 1 H), 5.70 (br s, 1 H), and 7.40–7.87 (m, 2 H). Anal. Calcd for $C_{13}H_{16}NO_2SBr$: C, 47.27; H, 4.89; N, 4.24. Found: C, 47.31; H, 4.90; N, 4.20.

A mixture containing 0.99 g of **31**, 0.87 g of tri-*n*-butyltin hydride, and 0.3 g of AIBN in 100 mL of benzene was heated at reflux for 10 h. Removal of the solvent under reduced pressure left an oily residue which was subjected to silica gel chromatography with a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 0.65 g (80%) of *N*-(phenylsulfonyl)-3-methylene-5-methylpiperidene (**32**) as a colorless oil: IR (neat) 3080, 2980, 2840, 1660, 1595, 1460, 1450, 1350, 1260, 1175, 1110, 1100, 1020, 975, 930, 860, and 800 cm^{-1}; NMR (benzene-d_6, 360 MHz) δ 0.52 (d, 3 H, J = 6.4 Hz), 1.13 (dd, 1 H, J = 13.4 and 12.0 Hz), 1.40–1.58 (m, 1 H), 1.83 (dd, 1 H, J = 13.4 and 4.0 Hz), 1.96 (dd, 1 H, J = 11.4 and 9.7 Hz), 2.88 (d, 1 H, J = 12.0 Hz), 3.50 (dd, 1 H, J = 11.4 and 3.8 Hz), 4.00 (d, 1 H, J = 12.0 Hz), 4.62 (s, 1 H), 4.74 (s, 1 H), 6.98–7.77 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.22 (q), 31.11 (d), 40.19 (t), 51.80 (t), 52.39 (t), 111.71 (t), 127.55 (d), 128.83 (d), 132.47 (d), 136.81 (s), and 139.99 (s). Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.11; H, 6.83; N, 5.57. Found: C, 61.99; H, 6.85; N, 5.56.

Preparation and Reaction of *N*,*N*-Bis(2-bromo-2-propenyl)benzenesulfonamide (33) with Tri-*n*-butyltin Hydride. A mixture containing 2.0 g of 2,3-dibromopropene, 1.58 g of benzenesulfonamide, and 1.40 g of potassium carbonate in 60 mL of anhydrous acetone was allowed to stir for 1 week at room temperature. The mixture was allowed to stir for 1 week at room temperature. The mixture was diluted with ether and washed with water followed by a saturated sodium chloride solution. The ether layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure. The unreacted benzene-

sulfonamide was removed by filtration, and the residue was chromatographed on a silica gel chromatography column with a 10% ethyl acetate–hexane mixture as the eluent. The major fraction isolated from the column contained 600 mg (52%) of *N,N*-bis(2-bromo-2-propenyl)benzenesulfonamide (**33**) as a colorless oil: IR (neat) 3080, 2920, 1630, 1480, 1450, 1350, 1150, 1090, 1060, 910, 780, 750, and 690 cm^{-1}; NMR ($CDCl_2$, 90 MHz) δ 4.13 (s, 4 H), 5.57 (br s, 2 H), 5.78 (br s, 2 H), and 7.4–7.9 (m, 5 H). Anal. Calcd for $C_{12}H_{1B}r_2NO_2S$: C, 36.47; H, 3.32; N, 3.55. Found: C, 36.47; H, 3.36; N, 3.53.

A mixture containing 790 mg of **33**, 1.28 g of tri-*n*-butyltin hydride, and 0.6 g of AIBN in 100 mL of benzene was heated at reflux for 10 h. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography with a 20% ethyl acetate–hexane mixture as the eluent. The major fraction contained 322 mg (67%) of a crystalline solid, mp 115–116 °C, whose structure was assigned as *N*-(phenylsulfonyl)-3,4-dimethyl-3-pyrrolidene (**35**) on the basis of its spectral properties: IR (KBr), 2960, 2920, 2840, 1590, 1480, 1450, 1350, 1310, 1250, 1170, 1110, 1080, 850, 770, 745, 700, 610, and 570 cm^{-1}; NMR (benzene-d_6, 360 MHz) δ 1.02 (s, 6 H), 3.80 (s, 4 H), 6.92–7.06 (m, 3 H), and 7.82–7.95 (m, 2 H). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.72; H, 6.38; N, 5.90. Found: C, 60.62; H, 6.41; N, 5.85.

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Ring-Extended Products from the Reaction of Epoxy Carbonyl Compounds and Nucleic Acid Bases

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Purine and pyrimidine bases react with epoxy carbonyl compounds in aqueous solution to yield ring-extended adducts. These products include etheno-modified bases as well as adducts in which the modification involves the formation of an additional six-membered ring. The latter examples are among the first known cases of this type of modification of pyrimidine bases. Plausible mechanisms for the formation of these adducts are discussed.

Epoxides occur widely in nature and have been identified in compounds from microorganisms and plants.[1-6] They are produced also in mammalian systems in the oxidation of polyunsaturated lipids.[7-9] The deleterious effects of some epoxy compounds are well documented. For example, aflatoxin B_1, sterigmatocystin, and the polycyclic aromatic hydrocarbons such as benzo[*a*]pyrene are known to be toxic and carcinogenic. Their detrimental effects are thought to be mediated by their conversion in vivo to their epoxides and subsequent modification of nucleic acid bases by these epoxides.[10-18] Simpler monofunctional epoxides have been known to modify nucleic acid bases.[19,20] In addition, the mode of formation and the detailed structures of adducts between carbonyl compounds and nucleic acid bases have been of considerable interest in studies of the constitution and mechanism of action of nucleic acids. Our interest in the modification of nucleic acid bases by malonaldehyde and related systems,[21,22] and in the synthesis of compounds related to the "Y" bases,[23] led us to examine such reactions with epoxy carbonyl compounds, the results of which are reported in this paper.

Results and Discussion

Very few studies have been undertaken to determine the detailed structures of adducts arising from the reaction of

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