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Utilization of Phenylthio Substituted Amines for the Synthesis of Pyrrolidines

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α-Phenylthio substituted amines [**2**, **10**, **17**, **26**, and **39**] have been found to be convenient reagents for the preparation of the pyrrolidine ring. Benzyl[(phenylthio)methyl][(trimethylsilyl)methyl]amine (**2**) undergoes 1,3-dipolar cycloaddition with several dipolarophiles in the presence of silver fluoride. The reaction is believed to proceed via the intermediacy of an azomethine ylide. Treatment of α-(phenylthio)cyanoamines **10** and **17** with strong base results in the loss of the phenylthio group, and formation of substituted *trans*-piperazines **21**, **22** in the case of **17**. The mechanism of the reaction involves dimerization of the initially formed cyano substituted azomethine ylide intermediate, which behaves as a captodative diradical. Finally, the reaction of several alkenyl[(phenylthio)methyl]amines with tributyltin hydride was studied as a method for generating the pyrrolidine ring via a radical cyclization reaction.

Anwendung von Phenylthio-substituierten Aminen zur Synthese von Pyrrolidinen

α-Phenylthio-substituierte Amine stellen leicht zugängliche Reagenzien zur Darstellung von Pyrrolidinringen dar. Benzyl[(phenylthio)methyl][(trimethylsilyl)methyl]amin (**2**) reagiert mit Dipolarophilen in Gegenwart von Silberfluorid unter Bildung von Pyrrolidinen, wobei wahrscheinlich eine Azomethinylid-Zwischenstufe durchlaufen wird. Die Behandlung der α-(Phenylthio)cyanamine **10** und **17** mit einer starken Base führt zum Verlust der (Phenylthio)gruppe, bei **17** unter Bildung substituierter *trans*-Piperazine **21**, **22**. Vermutlich kommt es zur Dimerisierung der ursprünglich gebildeten Cyan-substituierten Azomethinylid-Zwischenstufe über ein capto-dativ stabilisiertes Diradikal. Schließlich wurde die Reaktion einiger Alkenyl[(phenylthio)methyl]amine mit Tributylzinnhydrid als Darstellungsmethode für Pyrrolidinringsysteme durch radikalische Cyclisierung untersucht.

The preparation of pyrrolidines has received extensive attention by synthetic chemists in recent years, in part due to the interesting biological activities exhibited by several polysubstituted pyrrolidines[1]. Particularly useful general approaches to these heterocycles are the intramolecular ene strategy developed by *Oppolzer*[2,3], the electrophilic promoted cyclizations of unsaturated amine derivatives[4–7], and the tandem cationic aza-Cope-Mannich cyclization synthesis of *Overman*[8]. One of the most conceptually simple ways of pyrrolidine formation involves the 1,3-

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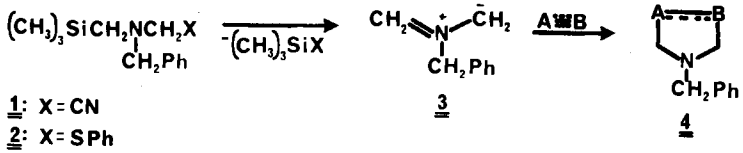
dipolar cycloaddition of an azomethine ylide with an olefin. Recent work in our laboratory has shown that (benzylamino)-α-cyanosilane **1** can act as an azomethine ylide equivalent when treated with silver fluoride in the presence of electron-deficient olefins[9,10]. We hoped that an analogous process would also occur with α-(phenylthio)aminosilane **2**. It would be particularly useful if the dipole could be generated without the use of silver salts. The research described herein was aimed at demonstrating the viability of α-phenylthio substituted amines as reagents for pyrrolidine synthesis.



1: X = CN
2: X = SPh

3

4

Results and Discussion

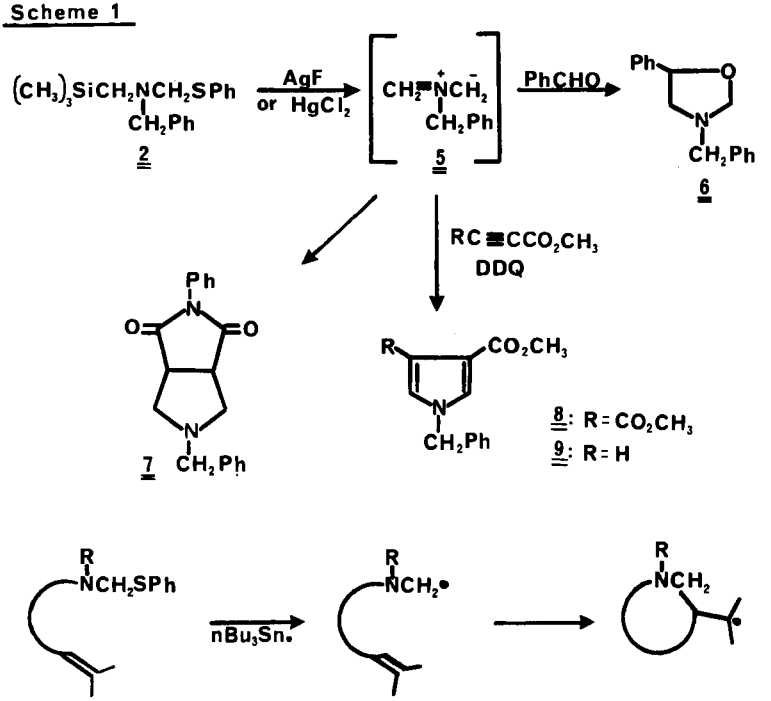
As outlined in this paper, we have found that α-phenylthio substituted amines are convenient reagents for the preparation of the pyrrolidine ring. Prior to launching into the synthesis of complex molecular systems using these reagents, we have designed and executed a number of model studies. The first system we investigated involved the use of benzyl[(phenylthio)methyl][(trimethylsilyl)methyl]amine (**2**) as an azomethine ylide precursor. Amine **2** was conveniently prepared in multigram quantities by treating benzylamine with (chloromethyl)trimethylsilane followed by reaction of the secondary amine with formaldehyde in the presence of thiophenol. A solution of **2** and dimethyl acetylenedicarboxylate in acetonitrile was allowed to react in the dark at 25 °C with a slight excess of silver fluoride. After oxidizing with DDQ, dimethyl 1-benzyl-3,4-pyrroledicarboxylate (**8**) was obtained in 62% yield. Similarly, treatment of **2** with silver fluoride in the presence of methyl propiolate produced pyrrole **9** in 65% yield. No attempts were made to isolate the initially produced dihydropyrroles. Cycloaddition of the dipole derived from **2** with *N*-phenylmaleimide and benzaldehyde was also studied and was found to produce cycloadducts **7** and **6** in 54 and 52% yield, respectively.

Efforts to liberate dipole **5** using other desilylating agents were not as rewarding[10]. Although the cycloaddition reaction occurred with mercuric chloride, the yields (30–50%) were much lower and a number of side products were also formed. No reaction occurred when lithium fluoride, zinc chloride, cesium fluoride, or cupric chloride were used as reagents for the key desilylation reaction. Since there was no significant improvement in the cycloaddition efficiency of **2** compared with the corresponding silylcyanoamine **1**, we decided to abandon further work with this system.

We thought it worthwhile to examine a route to pyrrolidines in which radical cyclization of an α-(phenylthio)amine plays a crucial role. Recent work by *Bachi*[11] and *Hart*[12] has shown that the reaction of tributyltin radical with (phenylthio)-lactams represents a convenient method for forming α-acylamino radicals. This led us to study the reaction of several alkenyl[(phenylthio)methyl]amines with

tributyltin hydride as a method for generating α-amino free radicals. Free radical cyclizations are attracting renewed interest from synthetic organic chemists for ring construction as traditional prejudices against free radical intermediates are removed[13–20]. 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[21–29]. 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[30]. It is very well documented and examples abound even in hetero atom analogues. The process is actually used as a probe for mechanisms[31–33], being diagnostic in rate[34] and regioselectivity for the radical but not for the ionic species[35,36]

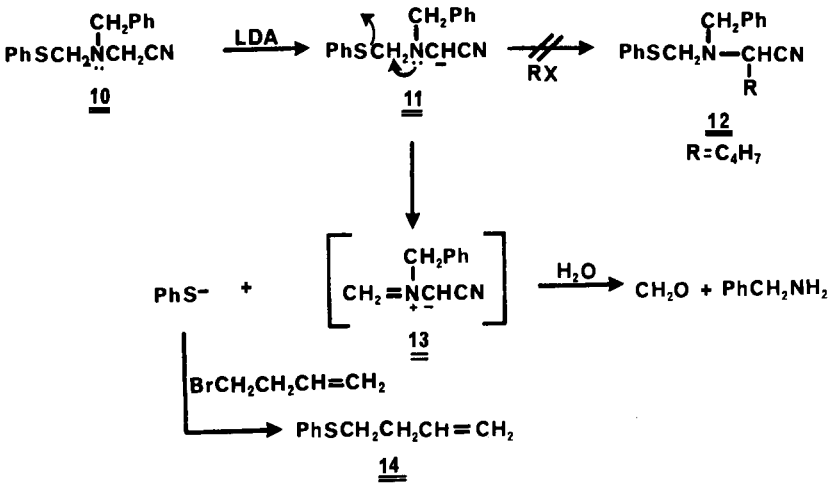
Scheme 1



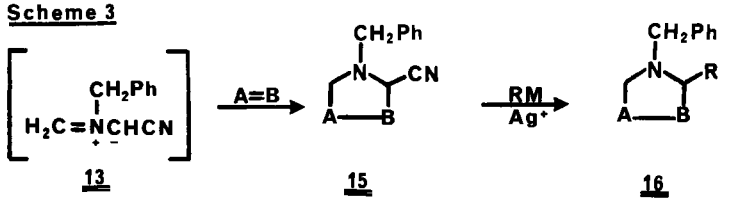
Our initial approach toward the synthesis of the desired alkenyl[(phenylthio)-methyl]amine system focused on the anion induced alkylation of aminonitrile **10**. The use of α-(dialkylamino)nitriles as masked acyl anion equivalents is well known[37]. Protected cyanoamines derived from aromatic aldehydes yield carbanions with strong bases such as LDA and the resulting anion undergoes ready alkylation[38]. We found, however, that treatment of aminonitrile **10** with LDA followed by reaction with 4-bromo-1-butene gave large quantities of 3-butenyl phenyl sulfide (**14**) but essentially none of the expected alkylated product **12**. Thus,

the presence of the phenylthio group dramatically affects the alkylation step. It is tempting to speculate that the initially formed carbanion **11** derived from **10** undergoes loss of the phenylthio moiety to give an azomethine ylide (**13**). More than likely the driving force for the elimination step is the result of a repulsion between the lone pair of electrons on the nitrogen atom with the resulting carbanion. We were struck by the fact that dipolar cycloaddition of the azomethine ylide **13** derived from **10** would be an extremely useful reaction since it should be easy to replace the cyano functionality of the pyrrolidine cycloadduct **15** by reaction with an appropriate organometallic reagent[39]. We decided to investigate the possible synthetic utilization of this cycloaddition, a process which can be schematized as in Scheme 3.

Scheme 2

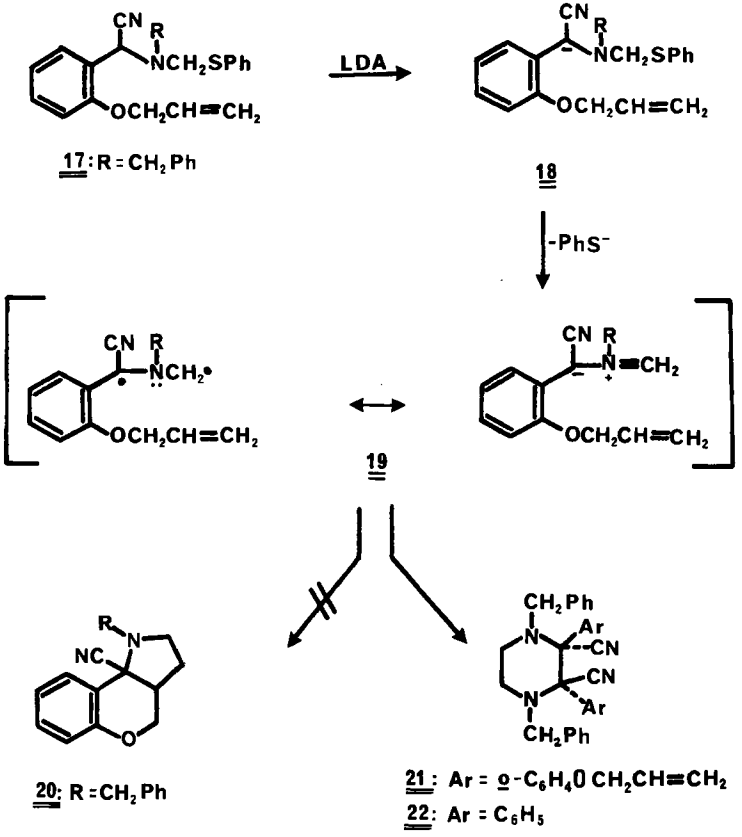


Scheme 3



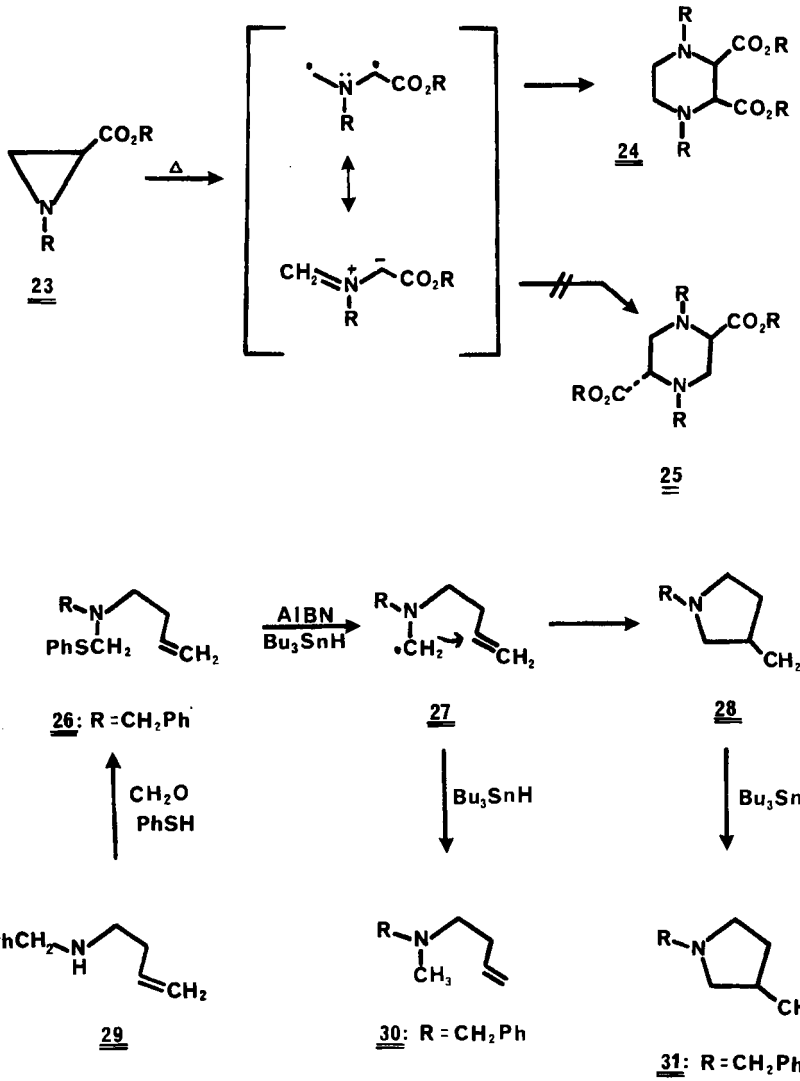
As is now well known, intramolecular dipolar cycloadditions have much synthetic potential[40,41]. The use of this reaction mode has increased in recent years and has proven valuable for the preparation of complex ring systems[42]. In order to trap the suspected azomethine ylide derived by the elimination of thiophenoxide from the aminonitrile carbanion, we examined the base induced reaction of [*o*-(allyloxy)phenyl]cyanoamine **17**. There are several reports in the literature which attest to the ready intramolecular dipolar cycloaddition that occurs with *o*-allyl-

salicylaldehyde derivatives[43–45]. All of our attempts, however, to isolate an intramolecular dipolar cycloadduct from the reaction of **17** with LDA failed. The only material which was isolated in 78% corresponded to *trans*-piperazine **21**. This base induced dimerization reaction seems to be quite general since treatment of the related (phenylthio)phenylcyanoamine with LDA afforded an analogous product **22**.



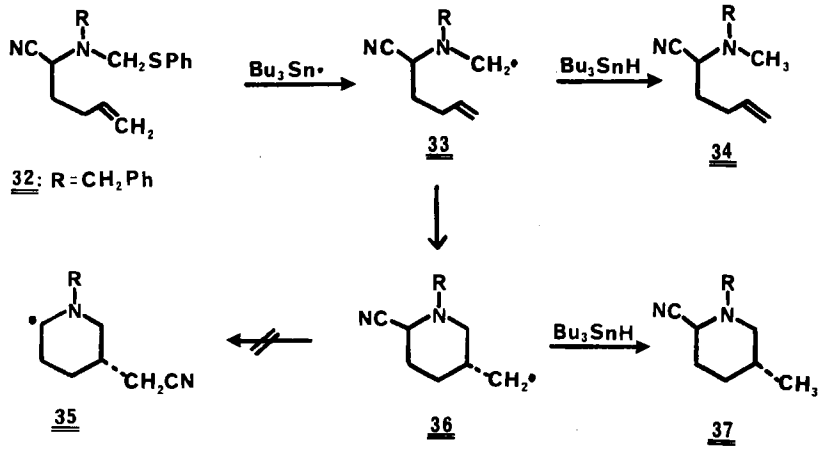
Thus, the cyano substituted azomethine ylide **19**, formed by thiophenoxide elimination from **18**, does not undergo typical intramolecular dipolar cycloaddition but rather undergoes ready dimerization, a reaction characteristic of a captodative radical. It is well known that free radicals can be stabilized by both electron acceptor and electron donor groups[46,47]. *Viehe* has pointed out that radicals which are substituted simultaneously by a donor and acceptor substituent enjoy particular stabilization[48]. Thus, azomethine ylides bearing captodative substituents are likely to behave more as a 1,3-diradical than a 1,3-dipole. An interesting example of this effect comes from the thermal dimerization of aziridine ester **23** which gives the "head-to-head" dimer **24** as the exclusive product[49,50]. This

behavior is most consistent with 1,3-diradical coupling since a dipolar species would have been expected to produce the other regioisomeric dimer **25**. In a related case, *Beugelmans* and coworkers found that benzyldimethylamine *N*-oxide also produced a "head-to-head" dimer when treated with a strong base[51]. These authors postulated the intermediacy of a 1,3-diradical which is formed from the initially produced carbanion followed by loss of OLi_2. All of our results, especially the absence of the traditional intramolecular dipolar cycloadduct in the reaction of **17** with base, are perfectly consistent with the hypothesis that piperazine **21** is derived from a captodative stabilized azomethine ylide.



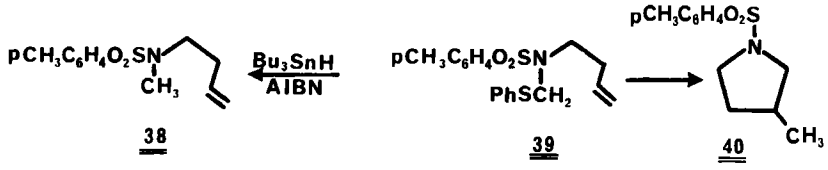
Since we were not able to prepare the desired alkenyl[(phenylthio)methyl]amine via the cyanoamine alkylation route, we decided to synthesize a representative α-thio substituted amine by an alternate procedure. Treatment of benzylamine with 4-bromo-1-butene gave benzyl(3-butenyl)amine (**29**) without complications. Reaction of this material with an aqueous formalin solution in the presence of thiophenol produced the desired thioamine **26**. Our initial studies focused on the generation of radical **27** by treatment of amine **26** with tributyltin hydride (1.4 equiv.) and AIBN (0.04 equiv.) in benzene at reflux. The only material isolated (89%) was the noncyclized amine **30**. This result is strikingly different from that encountered with the related α-acylamino radicals[11,12] where complete cyclization had occurred. It would seem 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[48].

Our attention was next given to the possible intramolecular cyclization of [(phenylthio)methyl]aminonitrile **32**. This compound was obtained in two straight-forward steps from 4-pentenal. Heating this aldehyde with benzylamine in the presence of potassium cyanide followed by a subsequent reaction of the initially formed aminonitrile with formalin and thiophenol gave **32** in 61% overall yield. The reductive cyclization of **32** was of particular interest since there are a number of examples in the literature where a cyano group is known to undergo rearrangement toward a radical center[52–55]. We were particularly interested in determining whether the rearrangement would take place with this system. Treatment of **32** with tributyltin hydride under the standard conditions gave mostly reduction product **34**. The structure of **34** was based on its spectral data and by comparison with an independently synthesized sample. The presence of small but significant quantities (i.e. 10–15%) of the cyclized *trans*-piperidine **37** was apparent from the appearance of a methyl doublet at $\delta = 0.89$ ($J = 6.5$ Hz). No signs of a cyano-rearranged product could be detected in the crude reaction mixture. Formation of the piperidine ring proceeds via a chair transition state thereby accounting for the *trans*-substituted product. The fact that cyclization does occur,



although to a limited degree, suggests that the reactivity of the α-amino radical center toward cyclization can be modified by a "remote" electron withdrawing group.

In an attempt to further define the scope of the thioamine radical cyclization and to promote the internal cycloaddition reaction, we studied the behavior of the closely related (phenylthio)sulfonamide system **39**. Placement of an electron withdrawing sulfonyl group on the nitrogen atom should retard the electronic assistance of the amino group with the radical center and enhance the radical cyclization. Our results are consistent with this expectation. The reductive cyclization of sulfonamide **39** afforded pyrrolidine **40** in 36% yield together with some of the noncyclized amine **38**. Although the cyclization of **39** was competitive with reduction, the low yield of pyrrolidine **40** imposes a serious limitation to the practicality of the method using butenyl substituted sulfonamides. It is clear that subtle electronic factors, which we do not fully understand, are involved in these cyclizations. Further studies dealing with the cyclization process and its application toward the synthesis of pyrrolidine containing alkaloids are in progress and will be reported on at a later date.



38 39 40

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Experimental Part

Melting points: Thomas-Hoover capillary melting point apparatus, uncorrected. – Infrared spectra: Perkin Elmer Model 283. – Proton NMR spectra: Varian EM-390 and Nicolet FT-360 spectrometer. – ^{13}C NMR spectra: IBM-200 MHz spectrometer. – Microanalyses: Atlantic Microlabs, Atlanta, Ga.-Mass spectra: Finnegan 4000 mass spectrometer, 70 eV.

N-[(Phenylthio)methyl]-N-[(trimethylsilyl)methyl]benzenemethanamine = Benzyl-[(phenylthio)methyl][(trimethylsilyl)methyl]amine (**2**): To a solution containing 4.0 g of benzyl[(trimethylsilyl)methyl]amine in 10 ml of tetrahydrofuran was added 2.84 g of thiophenol followed by 1.1 equivalents of an aqueous formaldehyde solution. The mixture was allowed to stir overnight and was then poured into water and extracted with ether. The ether layer was washed with water and was dried over magnesium sulfate. The ether was removed under reduced pressure leaving behind a yellow residue which was purified by silica gel chromatography using a 10% ethyl acetate/hexane mixture as the eluent. The

major fraction contained **2** (92%) as a clear oil. – IR (neat): 3000, 2990, 2800, 1590, 1485, 1370, 1250, 1125, 855, 745, and 700 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 0.10 (s, 9H), 2.12 (s, 2H), 3.63 (s, 2H), 4.45 (s, 2H), and 7.20 (m, 10H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ = −1.55, 40.84, 58.81, 66.79, 126.38, 127.15, 128.25, 128.88, 132.01, and 132.48. – MS: m/z = 315 (M^+), 149, and 91.

$C_{18}H_{25}NSSi$ (315.5) Calcd. C 68.51 H 7.99 N 4.44 Found C 68.64 H 7.94 N 4.40

General Procedure for the Cycloaddition Reactions of **2** *with Various Dipolarophiles:* To a stirred solution containing 300 mg of **2** in 5 ml of acetonitrile was added an equivalent quantity of the dipolarophile and 190 mg of silver fluoride. The solution was allowed to stir in the dark for 10 h and then was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The residue was purified on a silica gel chromatography (eluent 10–20% ethyl acetate/hexane). When dimethyl acetylenedicarboxylate and methyl propiolate were used as the dipolarophiles, the initially produced residue was oxidized to the corresponding pyrrole by heating with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene at 80°C for 12 h. The following cycloadducts were prepared according to the above procedure.

Dimethyl 1-Benzyl-3,4-pyrroledicarboxylate (**8**): Prepared in 62% yield as a yellow solid, m.p. 63–64°C. – IR (KBr): 3170, 3040, 2960, 1680, 1560, 1540, 1450, 1440, 1400, 1270, 1200, 1160, 1070, 970, 770, and 710 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 3.80 (s, 6H), 5.02 (s, 2H), and 7.1–7.4 (m, 7H). – UV (ethanol): 253 nm (ε 7500).

$C_{15}H_{15}NO_4$ (273.3) Calcd. C 65.92 H 5.53 N 5.13 Found C 65.86 H 5.51 N 4.86

Methyl 1-Benzyl-3-pyrrolecarboxylate (**9**) was prepared in 65% yield as a yellow solid, m.p. 51–52°C. – IR (KBr): 3160, 3040, 2960, 1710, 1650, 1540, 1500, 1450, 1370, 1250, 1200, 1120, 1070, 850, 760, 700 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 3.60 (s, 3H), 5.01 (s, 2H), 6.50 (m, 2H), 7.1–7.3 (m, 6H). – UV (ethanol): 232 (ε 11500), 249 nm (7000).

$C_{13}H_{13}NO_2$ (215.2) Calcd. C 72.54 H 6.09 N 6.51 Found C 72.49 H 5.91 N 6.43

7-Benzyl-3-phenyl-3,7-diazabicyclo[3.3.0]octane-2,4-dione (**7**) was prepared in 54% yield as a colorless oil. – IR (neat): 3145, 3000, 2950, 2900, 2800, 1760, 1700, 1575, 1490, 1445, 1380, 1340, 1310, 1265, 1200, 1155, 1130, 880, 840, 760, 740, and 700 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.3–2.7 (m, 2H), 3.2–3.6 (m, 4H), 3.60 (s, 2H), 7.0–7.7 (m, 10H). – MS: m/z = 306 (M^+), 149, 91.

$C_{19}H_{18}N_2O_2$ (306.3) Calcd. C 74.49 H 5.92 N 9.14 Found C 74.43 H 6.05 N 8.78

3-Benzyl-5-phenyloxazolidine (**6**) was prepared in 52% yield as a colorless oil. – IR (neat): 3100, 2850, 2700, 1590, 1490, 1440, 1340, 1300, 1140, 1060, 1020, 1000, 900, 860, 740, and 700 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.82 (dd, 1H, J = 12.0 and 8.0 Hz), 3.45 (dd, 1H, J = 12.0 and 7.0 Hz), 3.81 (s, 2H), 4.60 (s, 2H), 5.15 (dd, 1H, J = 8.0 and 7.0 Hz), 1–7.6 (m, 10H). – MS: m/z = 239 (M^+), 133, 132, 120, 110, 91.

$C_{16}H_{17}NO$ (239.3) Calcd. C 80.30 H 7.16 N 5.86 Found C 80.22 H 7.21 N 5.79

Preparation and Attempted Alkylation of Benzyl(cyanomethyl)[(phenylthio)methyl]-amine = [Benzyl[(phenylthio)methyl]amino]acetonitrile (**10**): To an ice cooled sample containing 1.10 g of thiophenol was added a 1.46 g sample of benzyl(cyanomethyl)amine followed by 0.81 g of a 37% aqueous formalin solution. The mixture was allowed to warm to room temperature and was then heated at 80°C for 2 h. After cooling to room temperature, the reaction mixture was diluted with ether, extracted with a saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography (eluent 5%

ethyl acetate/hexane). The major fraction isolated contained 1.86 g (69%) of **10** as a colorless oil. – IR (neat): 3070, 3040, 2940, 2825, 2460, 2440, 1620, 1590, 1500, 1480, 1440, 1375, 1270, 1140, 1075, 1025, 850, 740, 700, 650 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 3.60 (s, 2H), 3.80 (s, 2H), 4.28 (s, 2H), 7.07–7.57 (m, 10H). – UV (95% ethanol): 251 nm (ε 7800). – MS: m/z = 268 (M^+), 159, 109, 91 (base peak), 65.

$C_{16}H_{16}N_2S$ (268.4) Calcd. C 71.60 H 6.01 N 10.44 Found C 71.50 H 6.06 N 10.37

A solution containing 130 mg of **10** in 0.5 ml of anhydrous tetrahydrofuran was added dropwise to a solution containing one equivalent of lithium diisopropylamide and one equivalent of hexamethylphosphoric triamide in 5 ml of anhydrous tetrahydrofuran at –78°C. After stirring for 1 h, 0.06 ml of 1-butenyl bromide was added. The mixture was allowed to warm to room temp. and was stirred overnight. After standard workup, the residue was subjected to silica gel chromatography (eluent 20% ethyl acetate/hexane). The major fraction contained 89 mg (87%) of *4-(phenylthio)-1-butene* (**14**) whose spectral properties were identical with an authentic sample[56]. No other characterizable products could be obtained from the crude reaction mixture.

Benzyl[cyano[2-(2-propenyloxy)phenyl]methyl][(phenylthio)methyl]amine = α-[Benzyl[(phenylthio)methyl]amino]-2-(2-propenyloxy)benzeneacetonitrile (**17**): To a solution containing 1.43 g of benzylamine hydrochloride in 30 ml of tetrahydrofuran and 5 ml of water was added dropwise a solution containing 1.62 g of 2-(2-propenyloxy)benzaldehyde[57] in 2 ml of tetrahydrofuran. This was then followed by the dropwise addition of a solution containing 0.65 g of potassium cyanide in 5 ml of water. After the addition was complete, the reaction mixture was stirred at room temp. for 16 h. After standard workup, the residue was subjected to silica gel chromatography (eluent 10% ethyl acetate/hexane). The major fraction isolated from the column contained 2.16 g (78%) of *benzyl[cyano[2-(2-propenyloxy)phenyl]methyl]amine* as a colorless oil. – IR (neat): 3320, 3280, 3240, 2940, 2860, 2230, 1690, 1605, 1495, 1455, 1295, 1250, 1110, 1020, 1000, 925, 755, and 700 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.20 (br s, 1H), 3.90 (d, 1H, J = 12.0 Hz), 4.10 (d, 1H, J = 12.0 Hz), 4.57–4.63 (m, 2H), 4.87 (s, 1H), 5.20–5.50 (m, 2H), 5.83–6.23 (m, 1H), 6.83–7.42 (m, 9H). This material was used directly in the next step without further purification.

To a neat solution containing 2.19 g of the above amine at 0°C was added 0.81 ml of thiophenol followed by 0.64 g of a 37% aqueous formalin solution. The mixture was allowed to warm to room temp. and was then heated at 85°C for 3.5 h. The reaction mixture was cooled, diluted with ether, washed with a sodium hydroxide solution, a saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the resulting oil was subjected to silica gel chromatography (eluent 5% ether/hexane). The major fraction isolated from the plate contained 2.08 g (66%) of a pale yellow oil whose structure was assigned as **17** on the basis of its spectral properties. – IR (neat): 3080, 3040, 2940, 2880, 1690, 1605, 1495, 1455, 1290, 1250, 1110, 1025, 1000, 930, 750, 700 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 3.71 (d, 1H, J = 13.5 Hz), 4.11 (d, 1H, J = 13.5 Hz), 4.07–4.67 (m, 4H), 5.17–5.43 (m, 3H), 5.72–6.07 (m, 1H), 6.79–7.60 (m, 14H). – UV (95% ethanol): 340 (ε 1200), 253 nm (8940). – MS: m/z = 291, 172, 149 (base peak), and 91.

$C_{25}H_{24}N_2OS$ (400.5) Calcd. C 74.97 H 6.04 N 6.99 S 8.00
Found C 74.62 H 6.13 N 6.81 S 7.98

Reaction of **17** *with Lithium Diisopropylamide:* 0.33 ml of dry diisopropylamine in 50 ml of anhydrous tetrahydrofuran was treated at –20°C with 1.41 ml of a 1.48 M solution of *n*-butyllithium in hexane under nitrogen. After stirring for 20 min, 0.33 ml of anhydrous

hexamethylphosphoric triamide was added. The mixture was cooled to −78 °C and a solution containing 0.76 g of **17** in 3 ml of anhydrous tetrahydrofuran was added. After stirring for 2 h at −78 °C, the reaction mixture was allowed to warm to room temp. and was stirred for another 40 h. The solvent was removed under reduced pressure and the reaction mixture was diluted with ether. The ether solution was washed with water, a saturated sodium chloride solution and was dried over anhydrous magnesium sulfate. Removal of the solvent left a solid residue which was recrystallized from methylene chloride/hexane to give 415 mg (78%) of *1,4-dibenzyl-trans-2,3-bis[2-(2-propenyloxy)phenyl]-2,3-piperazinedicarbonitrile* (**21**) as a white crystalline solid: m.p. 174−175 °C. − IR ($CHCl_3$): 2930, 2840, 2800, 1680, 1605, 1490, 1450, 1290, 1125, 1015, and 995 cm^{-1}. − ^1H NMR ($CDCl_3$, 360 MHz): δ = 3.07 (d, 1H, *J* = 13.32 Hz), 3.40 (d, 1H, *J* = 10.8 Hz), 3.61 (d, 1H, *J* = 12.96 Hz), 3.78 (d, 1H, *J* = 13.32 Hz), 3.80 (br s, 1H), 4.04 (d, 1H, *J* = 13.32 Hz), 4.13 (d, 1H, *J* = 12.96 Hz), 4.25 (br s, 1H), 4.52−4.75 (m, 4H), 5.11−5.58 (m, 4H), 5.80−5.90 (m, 1H), 6.17−6.26 (m, 1H), 6.98−7.72 (m, 18H). − UV (95% ethanol): 274 nm (ε 4750). − MS: *m/z* = 355, 149 (base peak), 91, 84, 73.

$C_{38}H_{36}N_4O_2$ (580.7) Calcd. C 78.59 H 6.25 N 9.65 Found C 78.53 H 6.26 N 9.61

Benzyl(α-cyanobenzyl)[(phenylthio)methyl]amine = *α-[Benzyl[(phenylthio)methyl]-amino]benzeneacetonitrile* (**17**, H instead of $OCH_2CH=CH_2$): A solution containing 5.0 g of benzyl(α-cyanobenzyl)amine[58], 1.82 g of a 37% solution of formaldehyde, and 2.48 g of thiophenol was stirred at 80 °C for 9 h. Then the reaction mixture was extracted with ether and the organic layer was washed with a saturated sodium hydrogen carbonate solution and then dried over magnesium sulfate. The mixture was concentrated under reduced pressure to give 6.29 g (83%) of the product as a colorless oil. − IR (neat): 3020, 3015, 2810, 2720, 2215, 1720, 1590, 1500, 1480, 1460, 1370, 1205, 1100, 1070, 925, 750, 700 cm^{-1}. − ^1H NMR ($CDCl_3$, 90 MHz): δ = 3.49 (d, 1H, *J* = 13.0 Hz), 3.82 (d, 1H, *J* = 13.0 Hz), 4.03 (d, 1H, *J* = 13.0 Hz), 4.22 (d, 1H, *J* = 13.0 Hz), 5.30 (s, 1H), 7.10−7.40 (m, 15H).

$C_{22}H_{20}N_2S$ (344.5) Calcd. C 76.71 H 5.85 N 8.13 Found C 76.64 H 5.88 N 8.09

Reaction of the above Amine with Lithium Diisopropylamide: To a stirred solution containing 0.31 ml of diisopropylamine in 50 ml of tetrahydrofuran at −78 °C was added 1.28 ml of a 1.48 M solution of *n*-butyllithium. After stirring for 20 min, a 600 mg sample of the above amine was added followed by 0.3 ml of hexamethylphosphoric triamide. The mixture was stirred at −78 °C for 2 h and was then allowed to warm to room temperature. The solution was poured into water and extracted with ether. The ether layer was washed with water and dried over magnesium sulfate. Removal of the solvent left a dark residue which was subjected to silica gel chromatography (eluent 10% ethyl acetate/hexane). The major fraction contained 510 mg (63%) of a white solid, m.p. 180−181 °C, whose structure was assigned as *1,4-dibenzyl-trans-2,3-diphenyl-2,3-piperazinedicarbonitrile* (**22**), on the basis of its spectral properties. − IR (KBr): 3230, 3060, 2860, 1685, 1505, 1455, 1275, 1160, 1035, 750, 710 cm^{-1}. − ^1H NMR ($CDCl_3$, 90 MHz): δ = 3.30 (d, 1H, *J* = 12.0 Hz), 3.54 (d, 1H, *J* = 12.0 Hz), 3.77 (d, 1H, *J* = 11.0 Hz), 3.87 (d, 1H, *J* = 11.0 Hz), 4.06 (d, 2H, *J* = 12.0 Hz), 4.20 (d, 2H, *J* = 12.0 Hz), 6.9−7.4 (m, 20H).

$C_{32}H_{28}N_4$ (468.6) Calcd. C 82.05 H 5.98 N 11.96 Found C 81.86 H 5.86 N 11.83

N-(3-Butenyl)-N-[(phenylthio)methyl]benzenemethanamine (**26**): To a sample containing 35.7 g of benzylamine at 90 °C was added dropwise 15 g of 4-bromo-1-butene over 30 min. Afterwards 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 magnesium sulfate. The solvent was removed under reduced pressure and the residue was fractionally distilled through a Vigreux column under reduced pressure to give 9.59 g (53%) of *N-(3-butenyl)benzenemethanamine* (**29**), b.p. 105–107°C/7.5 Torr. – ^{1}H NMR (CCl_4, 90 MHz): δ = 1.02 (br s, 1H), 2.05–2.28 (m, 2H), 2.53–2.69 (m, 2H), 3.70 (s, 2H), 4.90–5.13 (m, 2H), 5.53–5.95 (m, 1H), 7.19 (s, 5H). – 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 **29** 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 temp. and was then heated at 80°C for 3 h. The mixture was cooled, 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 (eluent 1% ethyl acetate/hexane). The major fraction isolated contained 4.87 g (86%) of **26** as a colorless oil. – IR (neat): 3080, 3050, 2960, 2850, 1650, 1590, 1490, 1465, 1450, 1380, 1270, 1175, 1100, 1040, 925, 750, 705 cm^{-1}. – ^{1}H NMR (CCl_4, 90 MHz): δ = 2.0–2.25 (m, 2H), 2.68 (t, 2H, *J* = 7.5 Hz), 3.68 (s, 2H), 4.38 (s, 2H), 4.83–5.09 (m, 2H), 5.68 (ddt, 1H, *J* = 17.4, 9.45, and 6.3 Hz), 7.05–7.50 (m, 10H). – UV (95% ethanol): 240 nm (ε 6980). – MS: *m/z* = 283 (M^+), 174, 91 (base peak).

$C_{18}H_{21}NS$ (283.4) Calcd. 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 **26** *with Tributyltin Hydride:* A solution containing 1.0 g of **26**, 1.03 g of tributyltin hydride, and a catalytic amount of AIBN in 100 ml of anhydrous benzene was heated at reflux for 6 h under nitrogen. The solvent was removed under reduced pressure and the residue was subjected to silica gel flash chromatography (eluent 10% ethyl acetate/hexane). The major fraction contained 0.36 g (59%) of *N-(3-butenyl)-N-methylbenzenemethanamine* (**30**). – IR (neat): 3080, 3045, 3000, 2960, 2855, 2800, 1645, 1500, 1460, 1375, 1030, 920, 740, 700 cm^{-1}. – ^{1}H NMR (CCl_4, 90 MHz): δ = 2.13 (s, 3H), 2.17–2.50 (m, 2H), 3.42 (s, 2H), 4.87–5.13 (m, 4H), 5.77 (ddt, 1H, *J* = 17.4, 10.2, and 6.60 Hz), 7.19 (s, 5H). – MS: *m/z* = 175 (M^+), 174, 134, 92, 91 (base peak), 65.

$C_{12}H_{17}N$ (175.3) Calcd. C 82.23 H 9.78 N 7.99 Found C 82.27 H 9.80 N 7.90

The structure of **30** 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 (eluent 10% ethyl acetate/hexane) to give 1.39 g (79%) of **30** as a colorless oil which was identical in all respects with the sample obtained above.

2-[Benzyl[(phenylthio)methyl]amino]-5-hexenenitrile = N-(1-Cyano-4-pentenyl)-N-[(phenylthio)methyl]benzenemethanamine (**32**): To a solution containing 1.0 g of 4-pentenal[59] in 30 ml of tetrahydrofuran and 10 ml of water was added 1.71 g of benzylamine hydrochloride. After the salt had completely dissolved, a solution containing 0.77 g of potassium cyanide in 5 ml of water was added. The reaction mixture became cloudy and eventually separated into two phases. The mixture was vigorously stirred for 12 h and was then poured into water and extracted with ether. The ether extracts were washed with water, a saturated sodium chloride solution, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography with 20% ethyl acetate/hexane as the eluent. The major fraction isolated from the column contained 2.0 g (84%) of benzyl(1-cyano-4-pentenyl)amine as a colorless oil. – IR (neat): 3340, 3080, 3050, 2940, 2860, 2230, 1645, 1500, 1460, 1130, 1000, 920, 740, and 700 cm^{-1}. –

^{1}H NMR ($CDCl_3$, 90 MHz): δ = 1.50 (br s, 1H), 1.70–2.00 (m, 2H), 2.10–2.43 (m, 2H), 3.51 (t, 1H, *J* = 6.75 Hz), 3.80 (d, 1H, *J* = 12.75 Hz), 4.07 (d, 1H, *J* = 12.75 Hz), 4.93–5.20 (m, 2H), 5.77 (ddt, 1H, *J* = 17.7, 10.2, and 6.60 Hz), 7.33 (s, 5H).

To an ice-cooled sample of 1.0 g of the above amine was added 0.51 ml of thiophenol followed by 0.41 g of a 37% aqueous formalin solution. After warming to room temp., the mixture was heated at 80–85°C for 3 h. The mixture was cooled, diluted with ether, extracted with a saturated sodium chloride solution, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography (eluent 5% ethyl acetate/hexane). The major fraction contained 0.98 g (61%) of **32** as a colorless oil. – IR (neat): 3080, 3050, 2950, 2240, 1650, 1580, 1505, 1490, 1460, 1445, 1380, 1275, 1130, 1030, 920, 745, and 700 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 1.79–1.86 (m, 2H), 2.08–2.14 (m, 2H), 3.63 (d, 1H, *J* = 13.68 Hz), 3.88 (dd, 1H, *J* = 7.74 and 7.74 Hz), 4.06 (d, 1H, *J* = 13.68 Hz), 4.08 (d, 1H, *J* = 13.32 Hz), 4.30 (d, 1H, *J* = 13.32 Hz), 4.94–4.99 (m, 2H), 5.60–5.71 (m, 1H), 7.12–7.41 (m, 10H). – UV (95% ethanol): 225 nm (ε 7150). – MS: *m/z* = 213, 186, 91.

$C_{20}H_{22}N_2S$ (322.5) Calcd. C 74.49 H 6.88 N 8.69 S 9.94
Found C 74.76 H 6.93 N 8.65 S 9.97

Reaction of **32** *with Tributyltin Hydride:* A mixture containing 669 mg of **32**, 660 mg of tributyltin hydride and a catalytic amount of AIBN in 30 ml of anhydrous benzene was heated at reflux under nitrogen for 13 h. After cooling the reaction mixture to room temp., the solvent was removed under reduced pressure. Subjection of the residue to silica gel chromatography (eluent 2.5% ethyl acetate/hexane) gave 205 mg (46%) of a colorless oil, shown by NMR to contain a mixture of two compounds. Extensive silica gel chromatography (5% ethyl acetate/hexane) afforded a pure sample of *2-(benzylmethylamino)-5-hexenenitrile = N-(1-cyano-4-pentenyl)-N-methylbenzenemethanamine* (**34**). The structure of this material was assigned on the basis of its spectral data and by comparison with an authentic sample which was synthesized in the following fashion.

To a solution containing 1.0 g of benzyl(1-cyano-4-pentenyl)amine in 50 ml of anhydrous methylene chloride at 0°C under nitrogen was added 0.60 ml of methyl trifluoromethanesulfonate. After stirring for 30 min, the reaction mixture was warmed to room temp. and was stirred overnight. The mixture was then poured into a saturated sodium hydrogen carbonate solution and the two layers were separated. The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was distilled at 60–70°C/0.075 Torr to give 0.55 g (51%) of **34** as a colorless oil. – IR (neat): 3270, 3240, 2960, 2800, 2230, 1645, 1500, 1455, 1370, 940, 740, and 700 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 1.67–2.20 (m, 4H), 2.27 (s, 3H), 3.43 (d, 1H, *J* = 13.5 Hz), 3.53 (t, 1H, *J* = 7.5 Hz), 3.74 (d, 1H, *J* = 13.5 Hz), 4.88–5.12 (m, 2H), 5.47–5.91 (m, 1H), 7.28 (s, 5H). – MS: *m/z* = 214 (M^+), 213, 187, 146, 91 (base peak), 65.

$C_{14}H_{18}N_2$ (214.3) Calcd. C 78.46 H 8.46 N 13.08 Found C 78.36 H 8.46 N 13.04

The minor component obtained from the cyclization reaction could not be completely separated from amine **34**. The structure of this material is assigned as *trans-1-benzyl-5-methyl-2-piperidinecarbonitrile* (**37**) on the basis of a partial ^{1}H NMR spectrum (360 MHz) which showed a methyl doublet at δ = 0.89 (*J* = 6.5 Hz) and a doublet of doublets at 3.72 (*J* = 9.8 and 4.7 Hz) for the 2-H.

N-(3-Butenyl)-N-[(phenylthio)methyl]-p-toluenesulfonamide (**39**): A mixture containing 2.70 g of 4-bromo-1-butene, 2.76 g of anhydrous potassium carbonate, and 3.76 g of *p*-toluenesulfonamide in 60 ml of anhydrous acetone was heated at reflux for 30 h. The reaction

mixture was cooled, diluted with ether and washed with water and then with a saturated sodium chloride solution. The ether solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography (20% ethyl acetate/hexane as eluent). The first fraction contained 0.23 g (8%) of *N,N-di-3-butenyl-p-toluenesulfonamide* as a colorless oil. – IR (neat): 3950, 3000, 2840, 1650, 1605, 1500, 1460, 1340, 1160, 1095, 1000, 925, 820, 740, 660 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.15–2.38 (m, 4H), 2.42 (s, 3H), 3.12–3.28 (m, 4H), 4.93–5.18 (m, 4H), 5.73 (ddt, 2H, *J* = 17.7, 9.90, and 6.60 Hz), 7.28 (d, 2H, *J* = 8.25 Hz), 7.70 (d, 2H, *J* = 8.25 Hz). The second fraction contained 1.97 g (44%) of *N-(3-butenyl)-p-toluenesulfonamide* as a colorless oil. – IR (neat): 3285, 3080, 2980, 2935, 1645, 1600, 1500, 1425, 1325, 1160, 1090, 990, 920, 815, 660, and 550 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.07–2.30 (m, 2H), 2.43 (s, 3H), 2.92–3.15 (m, 2H), 4.67 (brt, 1H, *J* = 6.0 Hz), 4.92–5.13 (m, 2H), 5.67 (ddt, 1H, *J* = 18.6, 9.0, and 6.9 Hz), 7.27 (d, 2H, *J* = 8.25 Hz), 7.77 (d, 2H, *J* = 8.25 Hz).

A suspension containing 0.11 g of sodium hydride (50%) in 15 ml of anhydrous dimethylformamide was treated with 0.50 g of the above *N*-butenylsulfonamide in 2 ml of dimethyl formamide at room temp. under nitrogen. After the evolution of hydrogen had ceased, a solution containing 0.35 g of chloromethyl phenyl sulfide in 0.5 ml of dimethyl formamide was added. The reaction mixture was stirred at room temp. for 5.5 h. After standard workup, the oily residue was subjected to silica gel chromatography (10% ethyl acetate/hexane as eluent). The major fraction contained 0.67 g (87%) of **39** as a colorless oil. – IR (neat): 3080, 2990, 2940, 1645, 1600, 1580, 1440, 1345, 1310, 1160, 1090, 1000, 965, 920, 815, 740, 695, and 655 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.03–2.28 (m, 2H), 2.40 (s, 3H), 3.22–3.38 (m, 2H), 4.77–5.10 (m, 4H), 5.39–5.83 (m, 1H), 7.17–7.45 (m, 7H), 7.63 (d, 2H, *J* = 9.0 Hz). – UV (95% ethanol): 228 nm (ε 13800). – MS: *m/z* = 239, 198, 155, 91 (base peak), 65.

$C_{18}H_{21}NO_2S_2$ (347.4) Calcd. C 62.22 H 6.09 N 4.03 S 18.45
Found C 62.20 H 6.11 N 4.03 S 18.40

Reaction of **39** *with Tributyltin Hydride:* A solution containing 473 mg of **39**, 0.40 g of tributyltin hydride, and 0.20 g of AIBN in 100 ml of anhydrous benzene was heated at reflux under nitrogen. After 18 h, another small quantity of AIBN was added. The mixture was heated at reflux for another 11 h and was then cooled and the solvent was removed under reduced pressure. The resulting residue was subjected to silica gel chromatography (10% ethyl acetate/hexane as eluent). The first fraction contained 0.32 g of a tin containing substrate, the second fraction 136 mg (36%) of unreacted starting material. The third fraction contained 117 mg (36%) of *3-methyl-1-(4-methylphenylsulfonyl)pyrrolidine* (**40**), characterized by its 360 MHz ^1H NMR spectrum ($CDCl_3$): δ = 0.92 (d, 3H, *J* = 6.48), 1.30–1.40 (m, 1H), 1.86–1.95 (m, 1H), 2.03–2.16 (m, 1H), 2.43 (s, 3H), 2.75 (dd, 1H, *J* = 9.72 and 7.92 Hz), 3.22 (ddd, 1H, *J* = 9.72, 8.28, and 7.20 Hz), 3.34 (ddd, 1H, *J* = 9.72, 8.28, and 4.32 Hz), 3.42 (dd, 1H, *J* = 7.92 and 7.93 Hz), 7.31 (d, 2H, *J* = 8.28 Hz), 7.71 (d, 2H, *J* = 8.28 Hz).

The fourth fraction contained 62 mg (17%) of a clear oil whose structure was assigned as *N-(3-butenyl)-N-methyl-p-toluenesulfonamide* (**38**) on the basis of its spectral properties and by comparison with an independently synthesized sample: To a solution containing 0.17 g of *N*-(3-butenyl)-*p*-toluenesulfonamide in 10 ml of anhydrous dimethyl formamide was added 0.27 g of cesium carbonate under nitrogen at room temperature. After stirring for 15 min, 0.1 ml of methyl iodide was added. The mixture was stirred at room temp. for 20 h. After standard workup, the oily residue was distilled under reduced pressure (b. p. 70–75°C/0.075 Torr) to give 159 mg (88%) of analytically pure **38** as a colorless oil. – IR

(neat): 3090, 2990, 2940, 1645, 1605, 1550, 1460, 1340, 1160, 1080, 950, 820, 745, 720, and 669 cm^{-1}. – ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.13–2.36 (m, 2H), 2.43 (s, 3H), 2.73 (s, 3H), 2.98–3.15 (m, 2H), 4.93–5.16 (m, 2H), 5.75 (ddt, 1H, J = 18.0, 9.75, and 6.60 Hz), 7.28 (d, 2H, J = 8.40 Hz), 7.64 (d, 2H, J = 8.40 Hz). – UV (95% ethanol): 230 nm (ε 11200).

$C_{12}H_{17}NO_2S$ (239.3) Calcd. C 60.22 H 7.16 N 5.85 S 13.40
Found C 60.29 H 7.21 N 5.82 S 13.45

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