Activated Michael Acceptors as Precursors to Heterocycles. 1. 2-Azetidinones from 2-(Arylsulfonyl)propenoyl Chlorides and Amines

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The addition of NH_3 and other primary amines to *Z*-3-phenyl-2-(arylsulfonyl)propenoyl chlorides gives *trans*-2-arylsulfonyl-3-phenyl-2-azetidinones as the major product in addition to the corresponding 2-arylsulfonyl-3-phenylpropenamide. Electron-withdrawing substituents in the arylsulfonyl group increased the percentage of products derived from 1,4-addition relative to 1,2-addition, while electron-donating substituents increased the amount of 1,2-addition observed in the product mixture. Addition of α-methylbenzylamine gave a 68:32 mixture of the two diastereomers of the *trans*-azetidinone. The major diastereomer was identified as the 1-(1*R*)-(3*S*,4*S*) and 1-(1*S*)-(3*R*,4*R*) enantiomers **16a** by single-crystal X-ray crystallographic analysis. Phenylthio and phenylsulfoxo substituents did not promote 1,4-addition, although the addition of ammonia to *Z*-3-phenyl-2-(phenylsulfoxo)propenoyl chloride (**7a**) gave a 95:5 ratio of the corresponding propenamide **8a** and a 3-(phenylsulfoxo)azetidinone **9a**. *trans*-4-Phenyl-3-(arylsulfonyl)-2-azetidinones **12a** and **12c** were sulfonated by the pyridine−SO_3 complex to give the corresponding *N*-sulfonates **28** in >80% yield. The *p*-methoxybenzyl substituent of **15** was removed by ceric ammonium nitrate in CH_3CN to give **12a** in 70% yield.

The development of synthetic routes to monocyclic 2-azetidinones (β-lactams) was stimulated by the observation of antibacterial activity in monobactams and norcardicins.[1] While the interest in these materials as antibiotics has waned, 2-azetidinones have served as important intermediates in many other applications. They are precursors to β-amino alcohols and β-amino acids, useful building blocks for peptides containing nonprotein amino acids.[2−4] 2-Azetidinones have been used to introduce the C-13 side chain of the anticancer compound paclitaxel (taxol) and related analogues.[5] 2-Azetidinones have served as precursors to δ-lactones via N-to-O acyl migration as demonstrated in the total synthesis of the macrolide antitumor antibiotic Lankacidin C.[6] More recently, certain 2-azetidinones have displayed potent cholesterol absorption inhibitory activity.[7]

The synthetic approaches to 2-azetidinones are numerous.[8] Construction of the ring has included cyclization reactions of linear arrays of appropriate ring atoms as well as condensation and cycloaddition reactions of two, two-ring-atom pieces. Synthetic routes to 2-azetidinones from "one-pot" reactions of discrete one- and three-ring-atom components are less common and rarely involve the addition of an amine to a three-carbon unit.[9] In this manuscript, we describe a novel synthetic approach to 2-azetidinones involving the one-pot addition/cyclization

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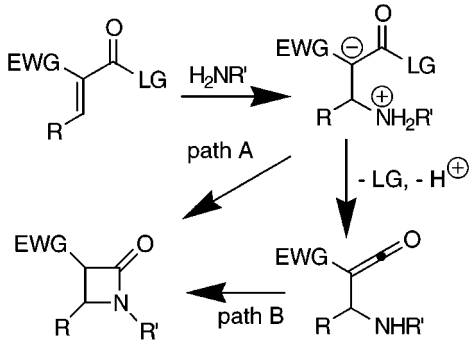
Scheme 1



of an amine to propenoic acid derivatives bearing an electron-withdrawing substituent at the 2-position.

Results and Discussion

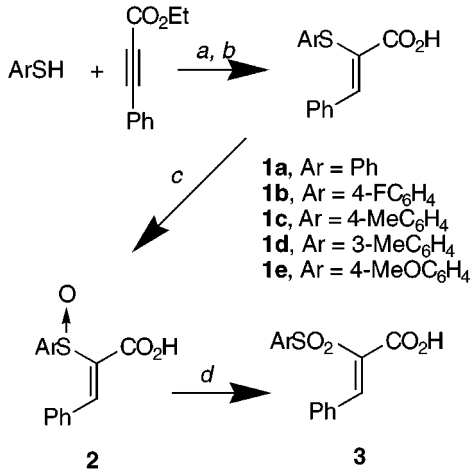
Typically, the addition of ammonia or a primary or secondary amine to a carboxylic acid derivative generates the corresponding amide. However, should the carboxylic acid derivative also be α,*β*-unsaturated, then both 1,2- and 1,4-addition of the amine are possible reaction pathways. In substrates that contain a second electron-withdrawing group (EWG) to stabilize the initial 1,4-adduct, one would expect 1,4-addition of the amine to be favored increasingly relative to 1,2-addition. Formation of 2-azetidinones from 1,4-addition of NH_3 and/or primary amines can be envisioned via two pathways as illustrated in Scheme 1. The zwitterionic intermediate formed by initial 1,4-addition might undergo proton transfer followed by cyclization to give 2-azetidinones (path A) or might eliminate the leaving group (LG) to form a ketene intermediate followed by ring closure to give 2-azetidinones (path B).

2-Phenylthio-, Phenylsulfoxo-, and Phenylsulfonyl-Substituted Propenoic Acid Derivatives. Our initial studies examined the addition of amines to 3-phenylpropenoic acid derivatives. Not surprisingly, the addition of NH_3 to a dioxane solution of *trans*-3-phenylpropenoyl chloride gave *trans*-3-phenylpropenamide and traces of *trans*-3-phenylpropenoic acid as the only detectable products by ^{1}H NMR. No formation of 2-azetidinones was observed.

Substituted 3-phenylpropenoyl chlorides were prepared bearing an electron-withdrawing group at the 2-position to stabilize an initial 1,4-adduct. The introduction of a 2-phenylthio substituent allowed the subsequent preparation of the electron-withdrawing sulfoxide and sulfone oxidation states.

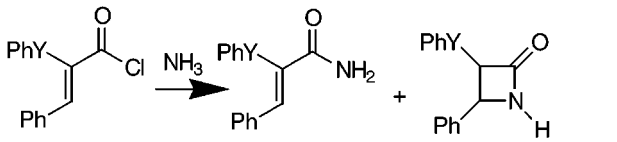
Z-3-Phenyl-2-(phenylthio)propenoic acid (**1a**) was prepared by the addition of thiophenol to ethyl phenylpropiolate followed by saponification of the resulting ethyl *Z*-3-phenyl-2-(phenylthio)propenoate (Scheme 2).[10] Oxidation of **1a** with hydrogen peroxide in the presence of

Scheme 2[a]



[a] Reagents: (a) neat, 25 °C; (b) KOH, aq EtOH; (c) Na_2WO_4, H_2O_2, aq dioxane; (d) *Oxone*, aq dioxane.

Scheme 3



4a, Y = S **5a**, Y = S (>99) **6a**, Y = S (<1)
7a, Y = SO **8a**, Y = SO (95±1) **9a**, Y = SO (5±1)
10a, Y = SO_2 **11a**, Y = SO_2 (16±1) **12a**, Y = SO_2 (84±1)

catalytic Na_2WO_4[11] gave *Z*-3-phenyl-2-(phenylsulfoxo)-propenoic acid (**2a**) in 86% yield. Sulfoxide **2a** was oxidized to *Z*-3-phenyl-2-(phenylsulfonyl)propenoic acid (**3a**) with *Oxone* ($2KHSO_3-KHSO_4-K_2SO_4$) in aqueous dioxane[12] in 94% isolated yield. Sulfone **3a** was also prepared in one pot from **1a** with *Oxone* in aqueous dioxane although the isolated yield (64%) was lower than with the two-step procedure. The propenoic acids **1a**−**3a** were converted to the corresponding acid chlorides (**4a**, **7a**, and **10a**, respectively) with oxalyl chloride.

The regiochemistry of NH_3 addition to the acid chlorides was affected by the 2-substituent with 1,4-addition increasing in the presence of electron-withdrawing groups (Scheme 3). The phenylthio substituent did not promote 1,4-addition of NH_3 to propenoyl chloride **4a**. Amide **5a** was isolated in 86% yield following addition of a dioxane solution of NH_3 to **4a**. The only observed products by ^{1}H NMR were **5a** and small amounts of propenoic acid **1a**. Azetidinone **6a** was not observed with a lower limit of detection of <1% by ^{1}H NMR.

The addition of a dioxane solution of NH_3 to phenylsulfoxo-substituted acid chloride **7a** gave a mixture of products from which amide **8a** was identified as the major component. Amide **8a** and a minor component [(95 ± 1):(5 ± 1) ratio, average of duplicate runs] were isolated as a mixture following chromatography on SiO_2. The minor component of the reaction mixture displayed signals in the ^{1}H NMR spectrum which were consistent with azetidinone **9a**: a broadened one-proton singlet at

(9) While one-pot procedures have not been described, numerous additions of amines to propenoate derivatives to give *β*-amino esters have been described. Subsequent cyclization of these intermediates in one or more steps has given 2-azetidinones. For recent examples: (a) Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274−6282. (b) Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1997**, 565−566. (c) Asao, N.; Uyehara, T.; Tsukada, N.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2103−2111. (d) Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am. Chem. Soc.* **1992**, *114*, 5427−5428.

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δ 7.06 (N*H*) and two coupled (J = 2.4 Hz, consistent with other *trans*-3-arylsulfoxo-4-phenyl 2-azetidinones[13]), one-proton doublets at δ 5.23 and 4.62 for the ring protons. We were unable to separate the two components in the sulfoxide oxidation state. However, oxidation of the product mixture with *Oxone* in aqueous dioxane gave phenylsulfonyl amide **11a** (vide infra) and *trans*-azetidinone **12a** (vide infra) in a 95:5 ratio. This mixture was separable via chromatography on SiO_2, and **11a** and *trans*-**12a** were isolated in 28% and 2% yields, respectively.

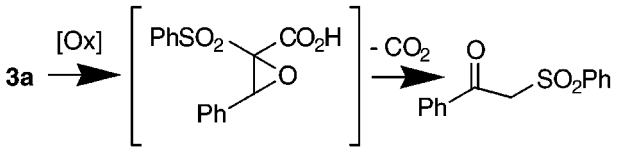
The addition of a dioxane solution of NH_3 to phenylsulfonyl-substituted acid chloride **10a** gave three isomeric products in a (16 ± 1):(80 ± 1):(4 ± 0) ratio by ^{1}H NMR (values are the average of duplicate runs). The first component was isolated in 15% yield after chromatography on SiO_2 and was identified as amide **11a**. The major component, isolated in 75% yield after chromatography on SiO_2 and recrystallization from EtOAc−hexanes, was identified as the *trans*-azetidinone **12a**. Similar results were obtained after the addition of an aqueous solution of NH_4OH to **10a** in dioxane. Azetidinone **12a** was isolated in 72% yield from a product mixture containing a 17:83 ratio of **11a** to *trans*-**12a**. None of the minor component was observed by ^{1}H NMR under these conditions.

The structure of *trans*-**12a** was established from its spectral and analytical data. Mass spectral and elemental analysis were consistent with a molecular formula of $C_{15}H_{13}NO_3S$. The ^{1}H NMR spectrum of *trans*-**12a** displayed, in addition to the expected aromatic protons, a broadened one-proton singlet (N-*H*) at δ 6.32 and two coupled, one-proton doublets (J = 2 Hz) at δ 5.26 and 4.38, respectively. The ^{13}C NMR spectrum of *trans*-**12a** displayed, in addition to the eight signals expected for the aromatic carbons, signals at δ 159.3, 79.4, and 53.4 consistent with the carbonyl carbon of an azetidinone (confirmed in the IR spectrum with $\nu_{C=O}$ 1791 cm^{-1}) and the two ring carbons, respectively. The 2-Hz coupling constant in the ^{1}H NMR spectrum is consistent with trans-substitution of the azetidinone ring and is in the 2−2.5-Hz range reported for other *trans*-3-arylsulfonyl- or 3-alkylsulfonyl-4-phenyl-2-azetidinones.[7a,14]

The minor component of the reaction mixture with anhydrous NH_3 in dioxane was isolated in 2% yield after careful chromatography. Spectroscopic data were consistent with the azetidinone ring. The ^{1}H NMR spectrum displayed two, coupled one-proton doublets at δ 5.46 and 4.40, respectively, with a 4.3-Hz coupling constant, which is consistent with a cis-3,4-disubstituted azetidinone (*cis*-**12a**).[8a] The observed selectivity for the trans-3,4-disubstituted azetidinone relative to the cis-isomer is 20:1 and is not surprising if steric interactions between the phenyl and phenylsulfonyl substituents are minimized in ring closure.

The phenylsulfonyl substituent promoted 1,4-addition of NH_3 to *Z*-3-phenyl-2-(phenylsulfonyl)propenoyl chloride (**10a**) relative to 1,2-addition with a reactivity ratio of 84:16, respectively, for the two processes. Of the products formed by 1,4-addition, the predominant product was *trans*-**12a**. No azetidinone products were observed from the addition of NH_3 to *Z*-3-phenyl-2-(phenylthio)propenoyl chloride (**4a**) while trace amounts of *trans*-azetidinone **9a** were detected in the addition of NH_3 to 3-phenyl-2-(phenylsulfoxo)propenoyl chloride (**7a**). In the latter system, there are two possible diastereomers of *trans*-azetidinone **9a** derived from the sulfoxide stereocenter. The individual diastereomers of the mixture could be neither distinguished by ^{1}H NMR spectroscopy nor isolated by chromatography.

Scheme 4



Substituent Effects in the 2-Arylsulfonyl Group. The 2-phenylsulfonyl group of **10a** promoted 1,4-addition to a much greater extent than either the phenylsulfoxo group of **7a** or the phenylthio group of **4a**. Electronic changes in the arylsulfonyl group also affected the extent of 1,4-addition with electron-withdrawing substituents giving increased chemoselectivity for 1,4-addition and electron-donating substituents giving decreased chemoselectivity.

The addition of commercially available *p*-fluorothiophenol, *p*-methylthiophenol, *m*-methylthiophenol, or *p*-methoxythiophenol to ethyl phenylpropiolate (as neat solutions of the two reagents) gave *Z*-3-phenyl-2-(arylthio)propenoic acids **1b**−**e**, respectively, following saponification of the initial ester with aqueous KOH in ethanol (Scheme 2).[10] While the strongly electron-withdrawing nitro substituent was desirable for this study, *p*-nitrothiophenol did not add to ethyl phenylpropiolate after 24 h as a neat solution at 50 °C. Oxidation of the sulfides to the sulfones **3** was best accomplished in two steps via initial oxidation to the sulfoxide followed by oxidation to the sulfone. Oxidation with hydrogen peroxide in the presence of catalytic Na_2WO_4 gave sulfoxides **2b**−**d** in 85%, 76%, and 63% yields, respectively.[11] The crude sulfoxides were converted directly to the arylsulfonyl compounds **3b**−**d** with *Oxone* in aqueous dioxane in 63%, 58%, and 39% isolated yields, respectively, from the sulfides.[12]

Sulfones **3** were also oxidized to other products under conditions that oxidized sulfoxides **2**. Further oxidation of **3a**−**d** to numerous products was observed upon prolonged reaction either with *Oxone* (15 h at reflux) or with hydrogen peroxide in the presence of catalytic Na_2WO_4 (15 h at reflux). For substrate **3a**, the major oxidation product was isolated in 20% yield and was identified as α-phenylsulfonyl acetophenone (Scheme 4). One possible route to the acetophenone derivative is epoxidation of **3a** to give an unstable epoxy carboxylic acid, which rearranges with loss of CO_2 to give the acetophenone derivative.

While further oxidation of **3a**−**d** was slow relative to the oxidation of the sulfide to sulfoxide or sulfoxide to sulfone, further oxidation of sulfone **3e** was competitive with oxidation of sulfoxide **2e** to sulfone **3e**. Sulfide **1e** was oxidized to **2e** in 40% yield with hydrogen peroxide in the presence of catalytic Na_2WO_4 although numerous other products were clearly present from the methoxy signals in the ^{1}H NMR spectrum of the reaction mixture. This suggests that oxidation of **2e** to **3e** is competitive with oxidation of **1e** to **2e**. Oxidation of **2e** either with

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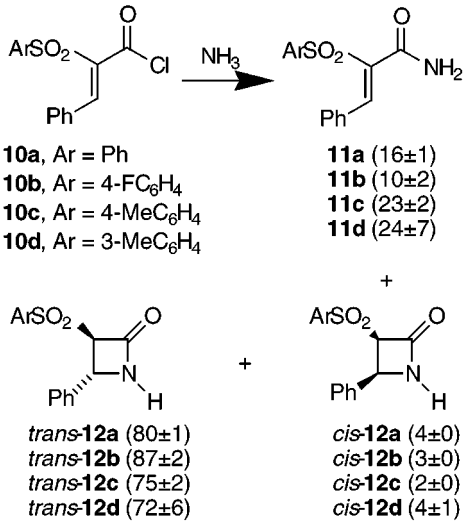
(14) Tokutake, N.; Miyake, M.; Kirisawa, M. *Synthesis* **1983**, 66−67.

Scheme 5



Oxone or with hydrogen peroxide in the presence of catalytic Na_2WO_4 did not give isolable yields of **3e**.

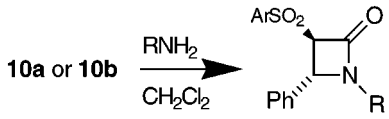
The carboxylic acids **3b**−**d** were converted to the acid chlorides **10b**−**d**, respectively, with oxalyl chloride in $CDCl_3$. The acid chlorides were used without further purification.

Addition of NH_3 (as a 1 M solution in dioxane) to anhydrous dioxane solutions of either **10b** or **10c** gave mixtures of the corresponding propenamides **11** and 2-azetidinones **12** as shown in Scheme 5. Signals consistent with *cis*-**12b** and *cis*-**12c** were observed by ^{1}H NMR, but these isomers were present as ≤3% of the product mixture. The electron-withdrawing fluoro substituent gave better selectivity for azetidinone formation than was observed for the phenyl substituent (Scheme 5, values are the average of duplicate runs). The electron-donating 4-methyl substituent gave poorer selectivity for 1,4-addition relative to the phenyl group. Although the substituent effects are not dramatic, the trends are consistent with the strength of the electron-withdrawing group determining the extent of 1,4-addition. *trans*-Azetidinones **12b** and **12c** were isolated in 85% and 73% yields, respectively.

The azetidinones were also produced by the condensation of NH_3 into CH_2Cl_2 solutions of acid chlorides **10**. Addition of liquid NH_3 to a CH_2Cl_2 solution of **10d** at ambient temperature gave a mixture of three isomeric products in a (72 ± 6):(24 ± 7):(4 ± 1) ratio (values are the averages of duplicate runs). The major product was identified as *trans*-**12d**, the unisolated, minor component was assigned the *cis*-azetidinone structure (C*H*'s as doublets at δ 5.56 and 4.31 with J = 4.5 Hz, CH_3 at δ 2.32), and the third component was amide **11d**. Compounds **11d** and *trans*-**12d** were obtained as crystalline solids in 11% and 66% isolated yields, respectively, after chromatography on SiO_2 and recrystallization from CH_3-CN.

Mechanistic Considerations. The amides **11** and azetidinones **12** were subjected to several control reactions. Both the propenamides **11** and 2-azetidinones **12** were thermally stable in refluxing dioxane. Propenamide **11a**, *trans*-2-azetidinone **12a**, and *cis*-2-azetidinone **12a** were all stable to the conditions of reaction (NH_3 in dioxane) for 24 h either at ambient temperature or at reflux. These controls suggest (1) that the azetidinone products are not formed via initial 1,2-addition of NH_3 to give propenamides **11** followed by intramolecular 1,4-addition, (2) that the azetidinone products are not formed by 1,4-addition of NH_3 to propenamides **11** followed by cyclization, (3) that the propenamides **11** are not derived from initial formation of azetidinones **12** followed by ring opening either thermally or in the presence of excess NH_3, and (4) that isomerization of *cis*- and *trans*-azetidinones **12** is not occurring under the reaction conditions.

Scheme 6



13, Ar = Ph, R = Me
14, Ar = Ph, R = PhCH$_2$
15, Ar = Ph, R = 4-MeOC$_6$H$_4$CH$_2$
16, Ar = Ph, R = PhCH(Me)
17, Ar = 4-FC$_6$H$_4$, R = PhCH$_2$

Two possible pathways for ring formation are shown in Scheme 1. Literature precedents for cyclizations of β-amino acid derivatives to 2-azetidinones as shown in path A have typically required added base and/or prolonged reaction times at reflux.[8a,15] For β-aminopropanoic acid chlorides, 2-azetidinones were isolated after 4 h in refluxing benzene with *N*,*N*-dimethylaniline as base.[16] Under the conditions of reaction for this study, the half-life for formation of 2-azetidinones from acid chlorides **10** (≈0.1 M) and excess NH_3 in dioxane (≈0.3 M) was <5 min at ambient temperature (reaction complete within 0.5 h). Attempts to monitor the progress of reaction by FT-IR showed the disappearance of starting material accompanied by the appearance of azetidinone and amide products. Following mixing of NH_3 and acid chloride **10a**, FT-IR spectra were recorded every 2.5 s for the first two minutes of reaction. No intermediates were detected in either the carbonyl or the ketene regions of the spectrum as **10a** was lost and **11a** and **12a** were formed. Although initial formation of a β-amino acid chloride derivative (Scheme 1, path A) cannot be rigorously excluded, the short half-life of reaction and absence of any detectable intermediates by FT-IR argue against this route. While these negative results are not conclusive, they suggest the formation of a highly reactive intermediate, which quickly cyclizes to give product. The formation of a ketene intermediate followed by intramolecular cyclization (Scheme 1, path B) is most consistent with these observations.

Addition of Other Amines. 2-Azetidinones were produced via the addition of a variety of primary amines to **10a**. With methylamine, benzylamine, *p*-methoxybenzylamine, and α-methyl benzylamine, *trans*-2-azetidinones were produced as ≥90% of the product mixture. The corresponding propenamide derivatives were observed as ≤8% of the product mixture by ^{1}H NMR and were not isolated from the product mixture. The *cis*-2-azetidinones were present as ≤2% of the product mixture.

The addition of methylamine to **10a** in CH_2Cl_2 gave *trans*-*N*-methyl azetidinone **13** in 37% isolated yield after chromatography on SiO_2 and recrystallization from EtOAc−hexanes (Scheme 6). (Propenoic acid **3a** was also

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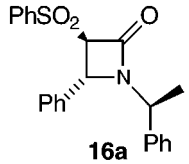
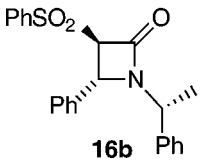
recovered in 25% yield.) The addition of benzylamine to a solution of **10a** in CH_2Cl_2 gave *N*-benzyl azetidinone **14** in 51% isolated yield after chromatography on SiO_2. Similar results were obtained upon the addition of *p*-methoxybenzylamine to **10a**. *N*-(*p*-Methoxybenzyl) azetidinone **15** was isolated in 65% yield after chromatography on SiO_2.

The addition of α-methyl benzylamine to **10a** offers the possibility of diastereoselection in the formation of the initial C−N bond. A 68:32 mixture (as determined by ^{1}H NMR) of two diastereomers of **16** was isolated from



16a



16b

1-(1*S*)-(3*R*, 4*R*) and 1-(1*R*)-(3*S*, 4*S*)

1-(1*R*)-(3*R*, 4*R*) and 1-(1*S*)-(3*S*, 4*S*)

the reaction mixture following the addition of α-methyl benzylamine to **10a**. The major diastereomer displayed two doublets at δ 4.78 and 4.34 (J = 2 Hz) for the *trans*-3,4-protons of the azetidinone ring. The benzylic methine of the 1-(1-phenylethyl) substituent appeared as a quartet at δ 4.33 coupled to a methyl doublet at δ 1.75 (J = 6.9 Hz). The minor diastereomer displayed two doublets at δ 4.80 and 4.36 (J = 2 Hz) for the trans-3,4-protons of the azetidinone ring and a benzylic methine for the 1-(1-phenylethyl) substituent as a quartet at δ 4.84 coupled to a methyl doublet at δ 1.32 (J = 7.1 Hz).

The unambiguous structural assignment of the major diastereomer as **16a** was made on the basis of single-crystal, X-ray diffraction analysis. Crystals of pure **16a** were obtained after recrystallization of the diastereomeric mixture from an EtOAc−hexanes (80:20) solution of the compound.[17] An ORTEP diagram showing the 1-(1*S*)-(3*R*,4*R*) stereochemistry is provided in Figure 1. The use of enantiomerically pure (*R*)- or (*S*)-α-methyl benzylamine (both of which are commercially available) would allow the preparation of optically active 2-azetidinones.

4-Fluorophenylsulfonyl propenoyl chloride **10b** reacted with benzylamine to give *N*-benzyl azetidinone **17** in 73% isolated yield.

Addition of Difunctional Amines. Difunctional amines such as 2-aminoethanol can form not only azetidinone and amide products but also other products involving the second functionality. The addition of 2-aminoethanol to propenoyl chloride **10a** could form either ester **18** via addition of the hydroxyl to the acid chloride of **10a** or amide **19** from addition of the amino group to the acid chloride. Either **18** or **19** could cyclize to form seven-membered heterocycles **20** or **21**, respectively, via intramolecular 1,4-addition (Scheme 7). Alternatively, 2-aminoethanol and **10a** could form the same seven-membered heterocycles via a combination of initial

(17) Crystal data for **16a**: $C_{23}H_{21}NO_3S$, M = 391.47, colorless needles, triclinic, space group $P\bar{1}$ (#2), a = 9.9188(3), b = 10.0498(2), c = 11.8120(4) Å, α = 68.321(2), β = 66.002(2), γ = 72.6360(10), V = 984.23(5) Å^3, Z = 2, D_c = 1.321 g cm^{-3}, μ = 1.88 cm^{-1}, T = 193 K. Data were collected on a Siemens SMART CCD Area Detector System using Mo Kα (λ = 0.71073) radiation, and the structure was solved by direct methods. Final discrepancy factors: R_1 = 4.13% and wR_2 = 9.60%. The authors have deposited the atomic coordinates for the crystal structure of **16a** with the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

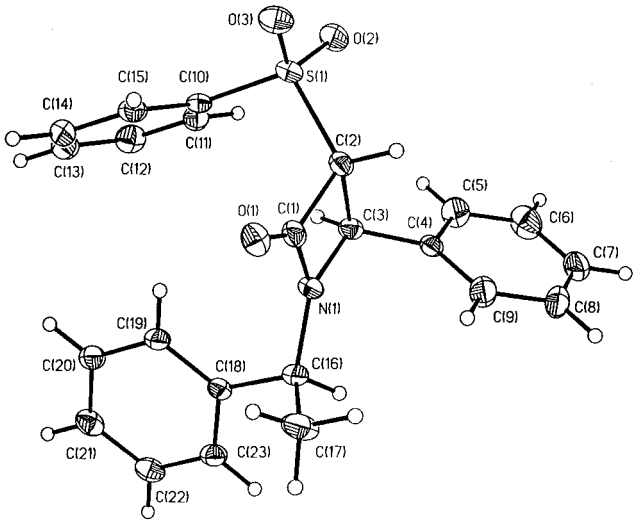
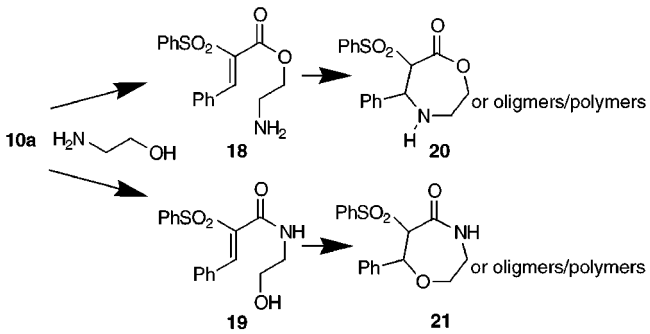
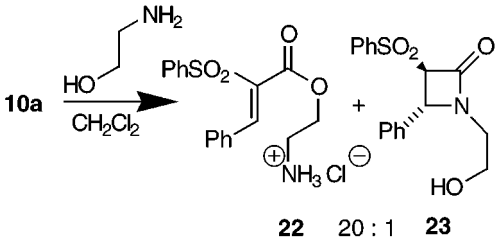


Figure 1. An ORTEP diagram of **16a** with thermal ellipsoids at the 50% probability level showing the 1-(1*S*)-(3*R*,4*R*) enantiomer.

Scheme 7



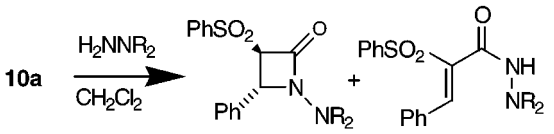
Scheme 8



1,4-addition followed by addition of the second functional group to the ketene or acid chloride intermediate. Other possible side reactions include oligomerization/polymerization from intermolecular reactions.

The addition of 2-aminoethanol to propenoyl chloride **10a** gave a 20:1 mixture of two products. The major product was not an azetidinone, but was presumed to be the ester **22** as shown in Scheme 8. Initial addition of the alcohol to the acid chloride to give **18** followed by scavenging of the HCl released during ester formation would give **22**. The ^{1}H NMR spectrum of the product mixture displayed a broadened three-proton singlet at δ 8.61 (−NH_3), a sharp one-proton singlet at δ 8.01 (C=C*H*-), a two-proton triplet at δ 3.68 (J = 5 Hz, −OCH_2-CH_2-), and a broadened, two-proton sextet at δ 3.39 (J = 5 Hz, −CH_2CH_2NH_3) in addition to the aromatic peaks expected for **22**. The ester carbonyl was observed in the IR spectrum with $\nu_{C=O}$ 1751 cm^{-1}. The ester **22** was unstable to heating and to chromatography on SiO_2

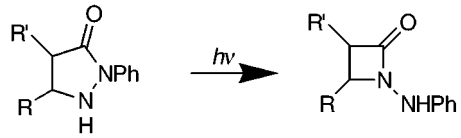
Scheme 9



perhaps giving oligomerization/polymerization reactions in both cases. Attempts to deprotonate the ammonium salt with $NaHCO_3$ gave similar oligomerization/polymerization reactions of the amine product.

The minor component of the product mixture was isolated in 3% yield by chromatography on SiO_2 eluted with 1:1 CH_2Cl_2/EtOAc and was identified as azetidinone **23**. In addition to the expected signals for the ring and the 3,4-substituents, the ^{1}H NMR spectrum of **23** was characterized by a two-proton multiplet centered at δ 3.82 ($-CH_2CH_2OH$) and two, one-proton, doublet-of-triplet patterns at δ 3.53 and 3.09 (J = 5, 15 Hz; NCH_2CH_2-) for the hydroxyethyl substituent. The hydroxyl proton appeared as a triplet at δ 2.91 and exchanged with D_2O. The IR spectrum of **23** displayed the expected signals for both alcohol and azetidinone with ν_{OH} of 3420 cm^{-1} and $\nu_{C=O}$ of 1763 cm^{-1}.

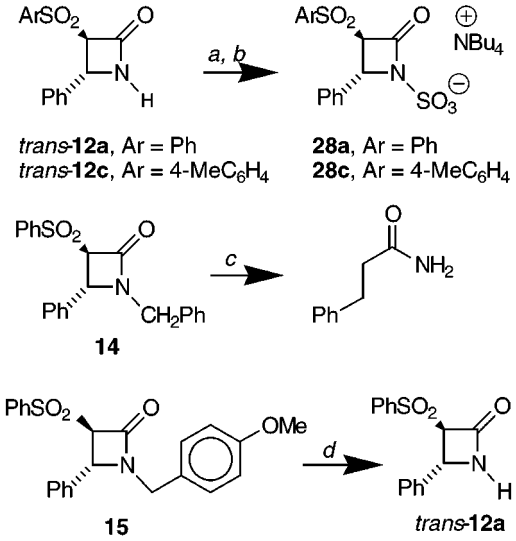
One literature precedent for the formation of azetidinones from 1,4-additions to propenoyl chlorides involved the addition of hydrazines.[18] The addition of *N*,*N*-dimethylhydrazine to propenoyl chloride derivatives (not bearing an electron-withdrawing group on the 2-position) was reported to give 1-(*N*,*N*-dimethylamino)-2-azetidinones.[18] The reported ^{1}H NMR spectrum at 40 MHz is not conclusive with respect to structure while the reported $\nu_{C=O}$ of 1582 cm^{-1} is seemingly inconsistent with a 2-azetidinone structure. 1-Amino-2-azetidinones have been prepared via the photochemical ring contraction of pyrazolidinones **24** (R = Me, R′ = H; R = H, R′ = Me).[19] 1-Amino-2-azetidinones **25** gave $\nu_{C=O}$ of 1760 cm^{-1} and



^{1}H NMR spectra consistent with the proposed azetidinone structures.[19]

Our systems bearing an electron-withdrawing group at the 2-position of the propenoyl chloride derivatives are more likely substrates for the formation of 1-amino-2-azetidinones upon reaction with hydrazine. However, neither *N*,*N*-dimethylhydrazine nor hydrazine addition to **10a** gave product mixtures that contained ^{1}H NMR or IR signals attributable to an azetidinone product **26** (Scheme 9). For *N*,*N*-dimethylhydrazine addition, the major product appeared to be **27** (R = Me) with a one-proton singlet at δ 7.82 (=C*H*−) and a six-proton singlet at δ 2.62 [$-N(CH_3)_2$] in the ^{1}H NMR spectrum and $\nu_{C=O}$ of 1702 cm^{-1} in the IR spectrum. Addition of hydrazine to **10a** did not give azetidinone products. The IR spectrum of this product mixture gave $\nu_{C=O}$ of 1636 cm^{-1}, which is inconsistent with either **26** or **27** (R = H). The

Scheme 10[a]



[a] Reagents: (a) Py-SO_3; (b) Bu_4NHSO_4; (c) Li or Na, NH_3; (d) ceric ammonium nitrate, CH_3CN.

propenoyl chlorides **10** appear to be poor substrates for the formation of 2-azetidinone products from hydrazine addition. This seemingly contradicts the literature report of 2-azetidinones from *N*,*N*-dimethylhydrazine and propenoyl chlorides.[18]

Reactions of *trans*-3-Arylsulfonyl-4-phenyl-2-azetidinones. We have examined a few reactions of *trans*-3-arylsulfonyl-4-phenyl-2-azetidinones from concern about the increased acidity of the proton at C-3 (Scheme 10). The water solubility of 2-azetidinones has been increased by N-sulfonation. *trans*-Azetidinones **12a** and **12c** reacted with the pyridine−SO_3 complex in pyridine to give sulfonate salts **28** in >80% yield following ion exchange with tetra-*n*-butylammonium hydrogensulfate.[20]

Reductive removal of the benzyl group of *N*-benzyl azetidinones has been reported with Li or Na in liquid NH_3.[21,22] However, reduction of *N*-benzyl azetidinone **14** with either Na or Li as limiting reagent in liquid NH_3 gave 3-phenylpropionamide in addition to unreacted azetidinone **14**. One can infer that the benzylic C−N bond of the azetidinone ring is easily reduced and that the phenylsulfonyl group is reductively removed as well under these conditions.

The *N*-*p*-methoxybenzyl substituent of **15** was oxidatively removed with ceric ammonium nitrate in CH_3CN to give azetidinone **12a** in 70% isolated yield.[23] There was no evidence for cis/trans isomerization at C-3 or for oxidation at C-3.

Summary and Conclusions

We have described a new synthetic approach to 2-azetidinones involving the 1,4-addition of amines to 3-phenylpropenoyl chlorides. In the absence of an electron-withdrawing group at the 2-position, only 1,2-addition

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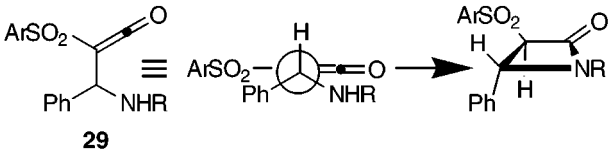
(22) Annunziata, R.; Benaglia, M.; Chiovato, A.; Cinquini, M.; Cozzi, F. *Tetrahedron* **1995**, *51*, 10025−10032.
(23) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C.-G. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413−1420.

Scheme 11



of the amine to the carbonyl of the acid chloride is observed. A 2-phenylthio substituent is not sufficiently electron withdrawing to divert 1,2-addition. However, a 2-phenylsulfoxo substituent gives a 95:5 ratio of 1,2- to 1,4-addition while a 2-phenylsulfonyl substituent gives a 16:84 ratio of 1,2- to 1,4-addition. The introduction of electron-withdrawing substituents on the arylsulfonyl group can increase the amount of 1,4-addition while electron-donating substituents can decrease the amount of 1,4-addition. No intermediates are detected during the reaction, which is suggestive that the initial 1,4-addition of the amine is followed by loss of chloride to generate a ketene intermediate **29** (Scheme 1, path B). As shown in Scheme 11, ring closure to give the *trans*-2-azetidinone would minimize steric interactions in the transition state leading to the final product. Both cis- and trans-isomers are stable to the reaction conditions, which suggests that the ring stereochemistry is set upon ring closure. The trans/cis selectivities observed in the reactions of this study are ≥20:1 with ammonia and are ≥50:1 with methylamine, benzylamine, and *p*-methoxybenzylamine, which is consistent with this model.

Experimental Section

General Methods. Solvents and reagents were used as received from Aldrich Chemical Co. Concentration in vacuo was performed on a Büchi rotary evaporator. NMR spectra were recorded at 30.0 °C on a Varian Gemini-300 instrument with residual solvent signal as internal standard: $CDCl_3$ (δ 7.26 for proton, δ 77.0 for carbon). Infrared spectra were recorded on a Perkin-Elmer FT-IR instrument. Elemental analyses were conducted by Atlantic Microanalytical, Inc.

General Procedure for the Preparation of *Z*-3-Phenyl-2-(arylthio)propenoic Acids. Preparation of *Z*-3-Phenyl-2-(4-fluorophenylthio)propenoic Acid (1b). *p*-Fluorothiophenol (2.56 g, 20.0 mmol) was added to ethyl phenylpropiolate (3.48 g, 20.0 mmol). The resulting solution was stirred for 1 h at ambient temperature (mildly exothermic). The resulting mixture was diluted with 50 mL of ethanol. Thirty milliliters of 10% KOH was added slowly over 30 min. The resulting mixture was heated at 50 °C for 1 h and was then diluted with 150 mL of cold water. The aqueous solution was extracted with ether (2 × 50 mL). The aqueous layer was acidified with 10% HCl precipitating a pale yellow solid. The solid was collected by filtration, washed with cold water, and air-dried. The crude acid was recrystallized from CH_3CN to give 5.15 g (94%) of **1b** as pale yellow crystals, mp 146.5−147 °C: ^{1}H NMR ($CDCl_3$) δ 9.5 (br s, 1 H), 8.23 (s, 1 H), 7.86 (m, 2 H), 7.41 (m, 3 H), 7.25 (m, 2 H), 6.95 (m, 2 H); IR (KBr) 3000 (br), 1680 cm^{-1}; EI MS, *m*/*z* 274.0489 (calcd for $C_{15}H_{11}FO_2S$ 274.0464). Anal. Calcd for $C_{15}H_{11}FO_2S$: C, 65.68; H, 4.04; S, 11.69. Found: C, 65.74; H, 4.04; S, 11.61.

The remaining acids **1** were prepared via the same procedure.

For *Z*-3-Phenyl-2-(phenylthio)propenoic Acid (1a): 83%; mp 139−139.5 °C (lit.[9] mp 139 °C).

For *Z*-3-Phenyl-2-(4-methylphenylthio)propenoic Acid (1c): 63%; mp 140−143 °C; ^{1}H NMR ($CDCl_3$) δ 10.2 (br s, 1 H), 8.25 (s, 1 H), 7.86 (m, 2 H), 7.41 (m, 3 H), 7.16 (d, 2 H, *J* = 8 Hz), 7.03 (d, 2 H, *J* = 8 Hz), 2.28 (s, 3 H); IR (KBr) 3000 (br), 1679 cm^{-1}; EI MS *m*/*z* 270.0729 (calcd for $C_{16}H_{14}O_2S$ 270.0715). Anal. Calcd for $C_{16}H_{14}O_2S-CH_3CN$: C, 69.42; H, 5.50. Found: C, 69.38; H, 5.28.

For *Z*-3-Phenyl-2-(3-methylphenylthio)propenoic Acid (1d): (46%) mp 104−106 °C; ^{1}H NMR ($CDCl_3$) δ 9.5 (br s, 1 H), 8.29 (s, 1 H), 7.87 (m, 2 H), 7.39 (m, 3 H), 7.13 (t, 1 H, *J* = 7.5 Hz), 7.05 (s, 1 H), 7.03 (d, 1 H, *J* = 7.5 Hz), 6.97 (d, 1 H, *J* = 7.5 Hz), 2.27 (s, 3 H); IR (KBr) 2950 (br), 1684 cm^{-1}; ES(−) MS *m*/*z* 269 ($C_{16}H_{14}O_2S-H$), 225 (M−H−CO_2). Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.11; H, 5.19. Found: C, 70.95; H, 5.27.

For *Z*-3-Phenyl-2-(4-methoxyphenylthio)propenoic Acid (1e): (80%) mp 133−136 °C; ^{1}H NMR ($CDCl_3$) δ 9.5 (br s, 1 H), 8.14 (s, 1 H), 7.87 (m, 2 H), 7.39 (m, 3 H), 7.23 (d, 2 H, *J* = 9 Hz), 6.78 (d, 1 H, *J* = 9 Hz), 3.75 (s, 3 H); IR (KBr) 2850 (br), 1678 cm^{-1}; ES(−) MS *m*/*z* 285 ($C_{16}H_{14}O_3S-H$), 241 (M−H−CO_2). Anal. Calcd for $C_{16}H_{14}O_3S\cdot CH_3CN$: C, 66.03; H, 5.23; N, 4.28. Found: C, 65.81; H, 4.92; N, 3.99.

Preparation of *Z*-3-Phenyl-2-(phenylsulfoxo)propenoic Acid (2a). Acid **1a** (5.12 g, 20.0 mmol) was dissolved in 100 mL of dioxane. To this solution was added a solution of $Na_2WO_4-2H_2O$ (0.20 g, 0.60 mmol) in 20 mL of pH 5.6 phosphate buffer (0.2 M). Hydrogen peroxide (4.0 mL of a 35% solution, 40 mmol) was added via syringe, and the resulting mixture was stirred for 15 h at ambient temperature. The reaction mixture was poured into 300 mL of water, and the products were extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified via chromatography on SiO_2 eluted with 30% ethyl acetate−hexanes. The product was recrystallized from CH_3CN to give 4.68 g (86%) of **2a** as a white crystalline solid, mp 145−147 °C: ^{1}H NMR ($CDCl_3$) δ 9.5 (br s, 1 H), 8.31 (s, 1 H), 7.51 (m, 2 H), 7.49 (m, 5 H), 7.34 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.2, 149.6, 140.2, 132.1, 131.8, 131.6, 131.1, 130.0, 129.7, 129.3, 124.8; IR (film on NaCl) 3050 (br), 1727, 1615 cm^{-1}; EI MS, *m*/*z* 272 (M^+, $C_{15}H_{12}O_3S$). Anal. Calcd for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44. Found: C, 66.13; H, 4.23.

Preparation of *Z*-3-Phenyl-2-(phenylsulfonyl)propenoic Acid (3a). *Oxone* (25 g) was added in 3 portions at 1-h intervals to a refluxing solution of **2a** (5.44 g, 20.0 mmol) in 100 mL of dioxane and 100 mL of water. After the final addition of *Oxone*, the reaction mixture was stirred at reflux for an additional 2 h. The reaction mixture was poured into 250 mL of water and the products were extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by chromatography on SiO_2 eluted with 30% ethyl acetate−hexanes to give 5.41 g (94%) of **3a** as a white crystalline solid, mp 70−73 °C: ^{1}H NMR ($CDCl_3$) δ 9.6 (br s, 1 H), 7.95 (s, 1 H), 7.93 (m, 2 H), 7.49 (m, 5 H), 7.34 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.6, 145.0, 140.4, 135.0, 134.2, 132.1, 131.9, 130.7, 129.6, 129.4, 129.1; IR (KBr) 3000 (br), 1727, 1615 cm^{-1}; FAB MS, *m*/*z* 289 (MH^+, $C_{15}H_{12}O_4S-H^+$), 244 (M−CO_2), 102 (base peak, HC≡CPh^+). Anal. Calcd for $C_{15}H_{12}O_4S$: C, 62.48; H, 4.20. Found: C, 62.59; H, 4.26.

Oxidation of 3a with *Oxone*. Preparation of α-Phenylsulfonyl Acetophenone. Sulfone **3a** (0.144 g, 0.500 mmol) and *Oxone* (1 g) were heated at reflux in 5 mL of dioxane and 5 mL of water for 15 h. Workup as described above for the preparation of **3a** gave a colorless glass, which was purified by chromatography on SiO_2 eluted with 30% ethyl acetate−hexanes to give 0.026 g (20%) of α-phenylsulfonyl acetophenone: ^{1}H NMR ($CDCl_3$) δ 7.90 (overlapping AA′BB′, 4 H), 7.53 (m, 6 H), 4.72 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 187.89, 135.85, 135.77, 134.26, 134.13, 129.26, 129.16, 128.82, 128.58, 63.58; IR (KBr) 1681 cm^{-1}; CI MS, *m*/*z* 261.0619 (calcd for $C_{14}H_{12}O_3S+H^+$ 261.0585).

General Procedure for the Oxidation of 2-Arylthiopropenoic Acids to 2-Arylsulfonylpropenoic Acids. 2-Arylthiopropenoic acids were oxidized in two steps to 2-arylsulfonylpropenoic acids **3b**−**d**. In the first step, the sulfide **1b**−**d** was oxidized to the sulfoxide **2b**−**d** as described above for **1a**. The crude sulfoxide product was oxidized to the sulfone with *Oxone* in aqueous dioxane as described above for **2a**. For characterization purposes, the sulfoxides were purified by

recrystallization from ethyl acetate−hexanes. Sulfide **1e** was oxidized to **2e** as described above for **1a**. The crude product was purified by chromatography on SiO_2 eluted with 30% EtOAc−CH_2Cl_2 and was recrystallized from CH_3CN.

For *Z*-3-Phenyl-2-(4-fluorophenylsulfoxo)propenoic Acid (2b): mp 125−128 °C (85% crude yield); ^{1}H NMR ($CDCl_3$) δ 10.2 (br s, 1 H), 8.31 (s, 1 H), 7.4−7.7 (m, 7 H), 7.23 (t, 2 H, J = 8 Hz); IR (KBr) 3000 (br), 1724, 1028 cm^{-1}; EI MS, *m*/*z* 290.0419 (calcd for $C_{15}H_{11}FO_3S$ 290.0413). Anal. Calcd for $C_{15}H_{11}FO_3S$: C, 58.81; H, 3.62. Found: C, 58.57; H, 3.51.

For *Z*-3-Phenyl-2-(4-fluorophenylsulfonyl)propenoic Acid (3b): mp 65−68 °C (63% overall from **1b**); ^{1}H NMR ($CDCl_3$) δ 6.3 (br s, 1 H), 8.20 (s, 1 H), 7.95 (dxd, 2 H, J = 5, 8 Hz), 7.51 (d, 2 H), 7.38 (m, 3 H), 7.18 (t, 2 H, J = 8 Hz); IR (KBr) 1744, 1323, 1150 cm^{-1}; EI MS, *m*/*z* 306.0349 (calcd for $C_{15}H_{11}FO_4S$ 306.0362). Anal. Calcd for $C_{15}H_{11}FO_4S$: C, 55.90; H, 3.44. Found: C, 56.01; H, 3.51.

For *Z*-3-Phenyl-2-(4-methylphenylsulfoxo)propenoic Acid (2c): mp 132−135 °C (76% crude yield); ^{1}H NMR ($CDCl_3$) δ 9.2 (br s, 1 H), 8.32 (s, 1 H), 7.83 (d, 2 H, J = 8 Hz), 7.49 (d, 2 H, J = 8 Hz), 7.29 (d, 2 H, J = 8 Hz), 2.39 (s, 3 H); IR (KBr) 3042 (br), 2550 (br), 1740, 1680, 1610 cm^{-1}; EI MS *m*/*z* 286.0678 (calcd for $C_{16}H_{14}O_3S$ 286.0664). Anal. Calcd for $C_{16}H_{14}O_3S$−CH_3CN: C, 66.03; H, 5.23. Found: C, 65.88; H, 5.03.

For *Z*-3-Phenyl-2-(4-methylphenylsulfonyl)propenoic Acid (3c): mp 75−78 °C (58% overall from **1c**); ^{1}H NMR ($CDCl_3$) δ 8.8 (br s, 1 H), 7.92 (s, 1 H), 7.95 (dxd, 2 H, J = 5, 8 Hz), 7.51 (m, 2 H), 7.38 (m, 3 H), 7.18 (t, 2 H, J = 8 Hz), 2.40 (s, 3 H); IR (KBr) 3180 (br), 1742, 1610 cm^{-1}; ES(−) MS *m*/*z* 302.0642 (calcd for $C_{16}H_{14}O_4S$ 302.0613). Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67. Found: C, 63.23; H, 4.90.

For *Z*-3-Phenyl-2-(3-methylphenylsulfoxo)propenoic Acid (2d): mp 88−90 °C (63% crude yield); ^{1}H NMR ($CDCl_3$) δ 9.3 (br s, 1 H), 8.34 (s, 1 H), 7.59 (m, 2 H), 7.50 (m, 3 H), 7.26−7.4 (m, 4 H), 2.38 (s, 3 H), (a CH_3CN of crystallization was observed as a singlet at δ 1.97); IR (KBr) 2950 (br), 1700, 1599 cm^{-1}; ES(−) MS *m*/*z* 285 ($C_{16}H_{14}O_3S$−H), 241 (M−H−CO_2). Anal. Calcd for $C_{16}H_{14}O_3S$−CH_3CN: C, 66.03; H, 5.23. Found: C, 65.88; H, 5.03.

For *Z*-3-Phenyl-2-(3-methylphenylsulfonyl)propenoic Acid (3d): mp 126−128 °C (39% overall from **1d**); ^{1}H NMR ($CDCl_3$) δ 8.5 (br s, 1 H), 8.30 (s, 1 H), 7.74 (m, 2 H), 7.52 (m, 2 H), 7.36−7.44 (m, 5 H), 2.40 (s, 3 H); IR (KBr) 3180 (br), 1747, 1610 cm^{-1}; EI MS *m*/*z* 302.0642 (calcd for $C_{16}H_{14}O_4S$ 302.0613). Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67. Found: C, 63.23; H, 4.90.

For *Z*-3-Phenyl-2-(4-methoxyphenylsulfoxo)propenoic Acid (2e): mp 122−124 °C (40%); ^{1}H NMR ($CDCl_3$) δ 11.4 (br s, 1 H), 7.93 (s, 1 H), 7.86 (d, 2 H, J = 9 Hz), 7.49 (d, 2 H, J = 8 Hz), 7.38 (m, 3 H), 3.84 (s, 3 H); IR (KBr) 1680, 1610 cm^{-1}; EI MS *m*/*z* 302.0642 (calcd for $C_{16}H_{14}O_4S$ 302.0613). Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67. Found: C, 63.33; H, 4.87.

General Procedure for the Preparation of Propenoyl Chlorides from the Corresponding Propenoic Acids. Preparation of *Z*-3-Phenyl-2-(4-fluorophenylsulfonyl)-propenoyl Chloride (10b). A solution of *Z*-3-phenyl-2-(4-fluorophenylthio)propenoic acid (**1b**, 0.612 g, 2.00 mmol) in 2 mL of $CDCl_3$ and 2 mL of oxalyl chloride was heated at reflux until conversion was complete (≈3 h). Reaction was initiated by the addition of 10 μL of *N*,*N*-dimethylformamide. The progress of the reaction was followed by ^{1}H NMR. When the reaction was complete, the reaction mixture was concentrated in vacuo and the *Z*-3-phenyl-2-(4-fluorophenylsulfonyl)propenoyl chloride (**10b**, 0.65 g, 100%) was used without further purification: ^{1}H NMR ($CDCl_3$) δ 8.28 (s, 1 H), 7.91 (dxd, 2 H, J = 5, 9 Hz), 7.40 (m, 4 H), 7.20 (m, 3 H).

For *Z*-3-Phenyl-2-(phenylthio)propenoyl Chloride (4a): see ref 10.

For *Z*-3-Phenyl-2-(phenylsulfoxo)propenoyl Chloride (7a): ^{1}H NMR ($CDCl_3$) δ 8.27 (s, 1 H), 7.87 (m, 2 H), 7.65 (m, 1 H), 7.56 (m, 2 H), 7.47 (m, 3 H), 7.43 (m, 3 H).

For *Z*-3-Phenyl-2-(phenylsulfonyl)propenoyl Chloride (10a): ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1 H), 7.85 (m, 2 H), 7.65 (m, 1 H), 7.55 (m, 2 H), 7.45−7.3 (m, 6 H).

For *Z*-3-Phenyl-2-(4-methylphenylsulfonyl)propenoyl Chloride (10c): ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1 H), 7.72 (AA′BB′, 2 H, J ("doublet") = 8 Hz), 7.3−7.5 (m, 7 H), 2.20 (s, 3 H).

For *Z*-3-Phenyl-2-(3-methylphenylsulfonyl)propenoyl Chloride (10d): ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1 H), 7.72 (m, 2 H), 7.4−7.5 (m, 7 H), 2.44 (s, 3 H).

General Procedures for the Addition of Ammonia to Propenoyl Chlorides. Method A. Preparation of *Z*-3-Phenyl-2-(phenylthio)propenamide (5a) by the Addition of Anhydrous Ammonia. To a solution of propenoyl chloride **4a** in 10 mL of dioxane (0.274 g; 1.00 mmol) was added 3 mL of a 1.0 M solution of ammonia in dioxane (3.0 mmol). The resulting solution was stirred at ambient temperature for 0.5 h and was then poured into 150 mL of water. The products were extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were washed with brine (2 × 25 mL), dried over $MgSO_4$, and concentrated. The residue was recrystallized from CH_3CN to give 0.22 g (86%) of **5a** as a yellow, crystalline solid: mp 145−146 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1 H), 7.80 (m, 2 H), 7.36 (m, 3 H), 7.24 (m, 5 H), 6.92 (br s, 1 H), 5.42 (br s, 1 H); IR (KBr) 1655, 1586 cm^{-1}; FAB MS, *m*/*z* 256 (MH^+, $C_{15}H_{13}OSN+H^+$). Anal. Calcd for $C_{15}H_{13}OSN$: C, 70.56; H, 5.10; N, 5.49; S, 12.56. Found: C, 70.63; H, 5.14; N, 5.53; S, 12.66.

Method B. Addition of Ammonium Hydroxide. To a solution of propenoyl chloride **4a** (0.274 g, 1.00 mmol) in dioxane (10 mL) was added 5 mL of a 28% ammonium hydroxide solution (exothermic). The resulting mixture was stirred for 0.5 h at ambient temperature. Workup as described gave 0.204 g (80%) of amide **5a**.

Method C. Addition of Liquid Ammonia. Propenoyl chloride **4a** (0.82 g, 3.0 mmol) was dissolved in dichloromethane (15 mL) in a flask equipped with a gas condenser containing a dry ice−2-propanol cooling bath. Approximately 0.5 g (≈30 mmol) of ammonia was condensed into the reaction mixture. The resulting solution was stirred at ambient temperature for 0.5 h. Workup as described gave 0.66 g (85%) of **5a**.

Addition of Ammonia to *Z*-3-Phenyl-2-(phenylsulfoxo)-propenoyl Chloride (7a). Phenylsulfoxo acid **2a** (0.272 g, 1.00 mmol) was dissolved in 3 mL of $CDCl_3$ and 3 mL of oxalyl chloride. The resulting solution was heated at reflux for 3 h until the starting acid was consumed. The reaction mixture was concentrated to give **7a**. Acid chloride **7a** (0.29 g, 1.0 mmol) in 10 mL of dioxane was treated with 3.0 mL of 1.0 M ammonia in dioxane as described for method A above. The crude product contained a 95:5 mixture of amide **8a** and azetidinone **9a**. Chromatography on SiO_2 eluted with 20% EtOAc−CH_2Cl_2 followed by recrystallization from CH_3CN gave 0.032 g (12%) of (phenylsulfoxo)propenamide **8a**: mp 99−102 °C; ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1 H), 7.80 (m, 2 H), 7.47 (m, 3 H), 7.32 (m, 3 H), 7.28 (m, 2 H), 6.93 (br s, 1 H), 6.35 (br s, 1 H); IR (KBr) 1665, 1586 cm^{-1}; EI MS, *m*/*z* 271.0735 (calcd for $C_{15}H_{13}O_2SN$ 271.0752). Anal. Calcd for $C_{15}H_{13}O_2SN$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.39; H, 4.91; N, 5.23.

The crude reaction mixture was oxidized with *Oxone* (1.5 g added in 0.5-g portions) as described above. The products were purified by chromatography on SiO_2 eluted with 20% EtOAc−CH_2Cl_2 to give 0.080 g (28%) of **11a** (vide infra) and 0.006 g (2%) of azetidinone **12a** (vide infra).

Addition of Ammonia to *Z*-3-Phenyl-2-(phenylsulfonyl)propenoyl Chloride (10a). Method A. Sulfone acid **3a** (0.576 g, 2.00 mmol) was dissolved in 3 mL of $CDCl_3$ and 3 mL of oxalyl chloride. The resulting solution was heated at reflux for ≈3 h until reaction was complete (monitored by ^{1}H NMR) and was concentrated to give **10a**. Acid chloride **10a** was dissolved in 20 mL of dioxane. To this solution was added 6.0 mL of a 1.0 M solution of ammonia in dioxane (6.0 mmol). The resulting solution was stirred 0.5 h at ambient temperature. The reaction mixture was poured into 150 mL of water, and the products were extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried

over $MgSO_4$, and concentrated. The products were separated by chromatography on SiO_2 eluted with 20% EtOAc−CH_2Cl_2 to give 0.086 g (15%) of propenamide **11a** (mp 177−178 °C from CH_3CN), 0.43 g (75%) of *trans*-azetidinone **12a** (mp 167−168 °C from CH_3CN), and 0.011 g (2%) of *cis*-azetidinone **12a** (mp 143−144 °C from CH_3CN).

For *Z*-3-Phenyl-2-(phenylsulfonyl)propenoyl Amide (11a): ^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2 H), 7.86 (s, 1 H), 7.45−7.65 (m, 5 H), 7.39 (m, 3 H), 6.42 (br s, 1 H), 5.70 (br s, 1 H); IR ($CHCl_3$) 1687, 1620 cm^{-1}; FAB MS, *m*/*z* 288 (MH^+, $C_{15}H_{13}O_3SN+H^+$). Anal. Calcd for $C_{15}H_{13}O_3SN$: C, 62.70; H, 4.56; N, 4.87. Found: C, 62.76; H, 4.61; N, 4.83.

For *trans*-4-Phenyl-3-(phenylsulfonyl)azetidin-2-one (*trans*-12a): ^{1}H NMR ($CDCl_3$) δ 8.03 (d, 2 H), 7.70 (m, 1 H), 7.59 (m, 2 H), 7.36 (m, 5 H), 6.32 (br s, 1 H), 5.26 (d, 1 H, J = 2 Hz), 4.38 (d, 1 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 159.3, 138.3, 137.2, 135.2, 130.0, 129.7, 129.6, 129.5, 126.3, 79.4, 53.4; IR (KBr) 2983, 1791 cm^{-1}; FAB MS, *m*/*z* 288 (MH^+, $C_{15}H_{13}O_3SN+H^+$). Anal. Calcd for $C_{15}H_{13}O_3SN$: C, 62.70; H, 4.56; N, 4.87. Found: C, 62.65; H, 4.60; N, 4.83.

For *cis*-4-Phenyl-3-(phenylsulfonyl)azetidin-2-one (*cis*-12a): ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 2 H), 7.63 (m, 3 H), 7.36 (m, 5 H), 7.05 (br s, 1 H), 5.46 (d, 1 H, J = 4.3 Hz), 4.40 (d, 1 H, J = 4.3 Hz); IR (KBr) 1788 cm^{-1}; FAB MS, *m*/*z* 288 (MH^+, $C_{15}H_{13}O_3SN+H^+$). Anal. Calcd for $C_{15}H_{13}O_3SN$: C, 62.70; H, 4.56; N, 4.87. Found: C, 62.81; H, 4.66; N, 4.85.

Addition of Ammonia to *Z*-3-Phenyl-2-(phenylsulfonyl)propenoyl Chloride (10a). Method B. Sulfone **3a** (0.576 g, 2.00 mmol) was dissolved in 3 mL of $CDCl_3$ and 3 mL of oxalyl chloride. The resulting solution was heated at reflux for ≈3 h until reaction was complete (monitored by ^{1}H NMR) and was concentrated to give **10a**. Acid chloride **10a** was dissolved in 20 mL of dioxane. To this solution was added 3.0 mL of a 28% ammonium hydroxide solution. Workup as described above for method A gave an 83:17 mixture of **12a** and **11a**. Separation as described gave 0.41 g (72%) of **12a** and 0.086 g (15%) of **11a**.

Addition of Ammonia to *Z*-3-Phenyl-2-(4-fluorophenylsulfonyl)propenoyl Chloride (10b). Method A. Sulfone **3b** (0.61 g, 2.0 mmol) was dissolved in 3 mL of $CDCl_3$ and 3 mL of oxalyl chloride. The resulting solution was heated at reflux for 1 h and was concentrated in vacuo to give acid chloride **10b**. Acid chloride **10b** in 20 mL of dioxane was treated with 6.0 mL of 1 M ammonia in dioxane as described. Workup and isolation by chromatography as described gave 0.030 g (5%) of amide **11b** as a white, crystalline solid (mp 100−103 °C from CH_3CN) and 0.52 g (85%) of azetidinone **12b** as a white, crystalline solid (mp 114.5−117.5 °C from CH_3CN).

For *Z*-3-Phenyl-2-(4-fluorophenylsulfonyl)propenamide (11b): ^{1}H NMR ($CDCl_3$) δ 8.05 (dxd, 2 H, J = 5, 9 Hz), 7.85 (s, 1 H), 7.39 (m, 2 H), 7.32 (m, 3 H), 7.27 (dxd, 2 H, J = 8, 9 Hz), 6.43 (br s, 1 H), 5.78 (br s, 1 H), (the CH_3CN of crystallization was observed as a singlet at δ 1.97); IR (KBr) 1655, 1586 cm^{-1}; FAB MS, *m*/*z* 306 (MH^+, $C_{15}H_{12}FO_3SN+H^+$). Anal. Calcd for $C_{15}H_{12}FO_3SN\cdot{}^1/_2CH_3CN$: C, 58.97; H, 4.18; N, 6.45. Found: C, 58.98; H, 4.34; N, 6.80.

For *trans*-4-Phenyl-3-(4-fluorophenylsulfonyl)azetidin-2-one (*trans*-12b): ^{1}H NMR ($CDCl_3$) δ 8.05 (dxd, 2 H, J = 5, 9 Hz), 7.40 (s, 5 H), 7.27 (dxd, 2 H, J = 8, 9 Hz), 6.42 (br s, 1 H), 5.29 (d, 1 H, J = 2.4 Hz), 4.37 (dxd, 1 H, J = 1.0, 2.4 Hz), (the CH_3CN of crystallization was observed as a singlet at δ 1.97); ^{13}C NMR ($CDCl_3$) δ 167.0 (d, J = 240 Hz), 159.2, 137.1, 132.6, 132.5, 129.8, 129.7, 126.3, 117.3 (d, J = 23 Hz), 79.4, 53.4; IR (KBr) 2927, 2855, 1797 cm^{-1}; FAB MS, *m*/*z* 306 (MH^+, $C_{15}H_{12}FO_3SN+H^+$), 262 (M−HNCO), 197 (M−HNCO−SO_2H). Anal. Calcd for $C_{15}H_{12}FO_3SN\cdot{}^1/_2CH_3CN$: C, 58.97; H, 4.18; N, 6.45. Found: C, 58.89; H, 4.36; N, 6.72.

Addition of Ammonia to *Z*-3-Phenyl-2-(4-methylphenylsulfonyl)propenoyl Chloride (10c). Method A. Sulfone **3c** (0.602 g, 2.00 mmol) was dissolved in 3 mL of $CDCl_3$ and 3 mL of oxalyl chloride. The resulting solution was heated at reflux for 1 h and was concentrated in vacuo to give acid chloride **10c**. Acid chloride **10c** in 20 mL of dioxane was treated with 6.0 mL of 1 M ammonia in dioxane as described. Workup and isolation by chromatography as described gave 0.11 g (18%) of amide **11c** as a white, crystalline solid (mp 99−102 °C from CH_3CN) and 0.46 g (75%) of azetidinone **12c** as a white, crystalline solid (mp 186−187 °C from CH_3CN).

For *Z*-3-Phenyl-2-(4-methylphenylsulfonyl)propenamide (11c): ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1 H), 7.80 (d, 2 H, J = 8 Hz), 7.39 (m, 3 H), 7.32 (d, 2 H, J = 8 Hz), 6.43 (br s, 1 H), 5.78 (br s, 1 H), 2.41 (s, 3 H); IR (KBr) 1655, 1586 cm^{-1}; EI MS, *m*/*z* 301.0810 (calcd for $C_{16}H_{15}O_3SN$ 301.0773). Anal. Calcd for $C_{16}H_{15}O_3SN$: C, 63.77; H, 5.02; N, 4.65. Found: C, 64.01; H, 4.86; N, 4.99.

For *trans*-4-Phenyl-3-(4-methylphenylsulfonyl)azetidin-2-one (*trans*-12c): mp 186−187 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (dxd, 2 H, J = 3, 8 Hz), 7.37 (dxd, 2 H, J = 3, 8 Hz), 7.35 (s, 5 H), 6.52 (br s, 1 H), 5.23 (d, 1 H, J = 2 Hz), 4.34 (d, 1 H, J = 2 Hz), 2.44 (s, 3 H); IR (KBr) 1788 cm^{-1}; EI MS, *m*/*z* 301.0810 (calcd for $C_{16}H_{15}O_3SN$ 301.0773). Anal. Calcd for $C_{16}H_{15}O_3SN$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.68; H, 5.08; N, 4.62.

Addition of Ammonia to *Z*-3-Phenyl-2-(3-methylphenylsulfonyl)propenoyl Chloride (10d). Method C. Sulfone **3d** (1.00 g, 3.31 mmol) was dissolved in 3 mL of $CDCl_3$ and 3 mL of oxalyl chloride. To the resulting solution was added 20 μL of *N*,*N*-dimethylformamide. The resulting solution was heated at reflux for 0.5 h. The reaction mixture was concentrated in vacuo to give **10d**. The residue was dissolved in 30 mL of CH_2Cl_2 and was treated with liquid ammonia as described. The products were separated by chromatography on SiO_2 eluted with 20% EtOAc−CH_2Cl_2 and recrystallized from CH_3CN to give 0.11 g (11%) of amide **11d** (mp 193−194 °C from CH_3CN) and 0.66 g (66%) of azetidinone **12d** (mp 165−166 °C from CH_3CN) as white, crystalline solids.

For *Z*-3-Phenyl-2-(3-methylphenylsulfonyl)propenamide (11d): ^{1}H NMR ($CDCl_3$) δ 7.87 (s, 1 H), 7.72 (m, 2 H), 7.61 (m, 2 H), 7.35−7.45 (m, 5 H), 6.48 (br s, 1 H), 5.74 (br s, 1 H), 2.43 (s, 3 H); IR (KBr) 3408, 1685 cm^{-1}; EI MS, *m*/*z* 301.0785 (calcd for $C_{16}H_{15}O_3SN$ 301.0773). Anal. Calcd for $C_{16}H_{15}O_3SN$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.58; H, 4.95; N, 4.63.

For *trans*-4-phenyl-3-(3-methylphenylsulfonyl)azetidin-2-one (*trans*-12d): ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 2 H), 7.50 (m, 2 H), 7.62 (m, 2 H), 7.38 (m, 5 H), 6.32 (br s, 1 H), 5.27 (d, 1 H, J = 2 Hz), 4.39 (d, 1 H, J = 2 Hz), 2.45 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.1, 139.7, 137.4, 136.7, 135.4, 129.2, 129.0, 128.94, 128.90, 125.9, 125.7, 78.5, 52.8, 21.2; IR ($CHCl_3$) 1770 cm^{-1}; EI MS, *m*/*z* 258 (M^+−HNCO). Anal. Calcd for $C_{16}H_{15}O_3SN$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.75; H, 5.03; N, 4.70.

General Procedure for the Addition of Primary Amines to *Z*-3-Phenyl-2-(phenylsulfonyl)propenoyl Chloride (10a). A solution of amine (2 equiv) in CH_2Cl_2 (5 mL/mmol) was added to a solution of **10a** in CH_2Cl_2 (5 mL/mmol) at ambient temperature. After the addition was complete, the reaction mixture was stirred at ambient temperature for 0.5 h. The reaction mixture was diluted with CH_2Cl_2, and the resulting solution was washed with cold, 3 N HCl (3×), saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on SiO_2 (30−50% EtOAc−hexanes), and the azetidinones were recrystallized from CH_3CN.

For *trans*-1-Methyl-4-phenyl-3-(phenylsulfonyl)azetidin-2-one (13): 37%; mp 153−155 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (dxd, 2 H, J = 2, 8 Hz), 7.68 (t, 1 H, J = 7.5 Hz), 7.57 (t, 2 H, J = 7.8 Hz), 7.38 (m, 2 H), 7.25 (dxd, 2 H, J = 2, 7.5 Hz), 5.02 (d, 1 H, J = 2 Hz), 4.32 (d, 1 H, J = 2 Hz), 2.84 (s, 3 H); IR (KBr) 2983, 1767 cm^{-1}; EI MS, *m*/*z* 301.0810 (calcd for $C_{16}H_{15}O_3SN$ 301.0773). Anal. Calcd for $C_{16}H_{15}O_3SN$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.65; H, 4.80; N, 4.83.

For *trans*-1-Benzyl-4-phenyl-3-(phenylsulfonyl)azetidin-2-one (14): 51%; mp 153−155 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (dxd, 2 H, J = 2, 8 Hz), 7.68 (t, 1 H, J = 7.5 Hz), 7.56 (t, 2 H, J = 7.8 Hz), 7.35 (m, 3 H), 7.25 (m, 3 H), 7.21 (m, 2 H), 7.03 (m, 2 H), 4.85 (d, 1 H, J = 15.1 Hz), 4.82 (d, 1 H, J = 2 Hz), 4.41 (d, 1 H, J = 2 Hz), 3.81 (d, 1 H, J = 15.1 Hz); ^{13}C NMR ($CDCl_3$) δ 158.8, 137.8, 134.6, 134.5, 133.8, 129.3, 129.2, 129.0, 128.9, 128.2, 128.0, 126.6, 76.6, 55.8, 45.2; IR (KBr) 3001, 1765

cm^{-1}; EI MS, *m/z* 377.1716 (calcd for $C_{22}H_{19}O_3SN$ 377.1086). Anal. Calcd for $C_{22}H_{19}O_3SN$: C, 70.00; H, 5.07; N, 3.71. Found: C, 69.98; H, 5.03; N, 3.83.

For *trans*-1-(*p*-Methoxybenzyl)-4-phenyl-3-(phenylsulfonyl)azetidin-2-one (15): 65%; mp 153−155 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 2 H, J = 8 Hz), 7.68 (t, 1 H, J = 8 Hz), 7.52 (t, 2 H, J = 8 Hz), 7.32 (m, 3 H), 7.17 (m, 2 H), 6.92 (d, 2 H, J = 8 Hz), 6.76 (d, 2 H, J = 8 Hz), 4.77 (d, 1 H, J = 15.1 Hz), 4.78 (d, 1 H, J = 2 Hz), 4.39 (d, 1 H, J = 2 Hz), 3.74 (s, 3 H), 3.73 (d, 1 H, J = 15.1 Hz); IR (KBr) 2350, 1763 cm^{-1}; EI MS, *m/z* 407 ($C_{23}H_{21}O_4SN$). Anal. Calcd for $C_{23}H_{21}O_4SN$: C, 67.79; H, 5.19; N, 3.44. Found: C, 67.65; H, 5.19; N, 3.43.

For (1*S*,3*R*,4*R*)- or (1*R*,3*S*,4*S*)-*trans*-1-(1-Phenylethyl)-4-phenyl-3-(phenylsulfonyl)azetidin-2-one (16a): 36%; mp 185−187 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (dxd, 2 H, J = 2, 8 Hz), 7.67 (t, 1 H, J = 7.5 Hz), 7.58 (t, 2 H, J = 7.8 Hz), 7.45 (m, 1 H), 7.2−7.45 (m, 7 H), 7.08 (m, 4 H), 4.78 (d, 1 H, J = 2 Hz), 4.34 (d, 1 H, J = 2 Hz), 4.33 (q, 1 H, J = 6.9 Hz), 1.75 (d, 3 H, J = 6.9 Hz); IR (CH_2Cl_2) 1763 cm^{-1}; EI MS, *m/z* 391.1277 (calcd for $C_{23}H_{21}O_3SN$ 391.1242). Anal. Calcd for $C_{23}H_{21}O_3SN$: C, 70.56; H, 5.41; N, 3.58. Found: C, 70.61; H, 5.19; N, 3.71.

***trans*-1-Benzyl-4-phenyl-3-(4-fluorophenylsulfonyl)-azetidin-2-one (17):** 65%; mp 153−155 °C; ^{1}H NMR ($CDCl_3$) δ 8.01 (dxd, 2 H, J = 5, 9 Hz), 7.35 (m, 3 H), 7.15−7.35 (m, 7 H), 7.04 (m, 2 H), 4.85 (d, 1 H, J = 15.1 Hz), 4.82 (d, 1 H, J = 2 Hz), 4.39 (d, 1 H, J = 2 Hz), 3.80 (d, 1 H, J = 15.1 Hz); IR (KBr) 1775 cm^{-1}; EI MS, *m/z* 395.0964 (calcd for $C_{22}H_{18}FO_3SN$ 395.0991). Anal. Calcd for $C_{22}H_{18}FO_3SN$: C, 66.82; H, 4.59; N, 3.54. Found: C, 66.91; H, 4.60; N, 3.55.

***trans*-1-(2-Hydroxyethyl)-4-phenyl-3-(phenylsulfonyl)-2-azetidinone (23):** 3%; mp 85−88 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 2 H, J = 8 Hz), 7.72 (t, 1 H, J = 8 Hz), 7.61 (t, 2 H, J = 8 Hz), 7.41 (m, 3 H), 7.31 (m, 2 H), 5.16 (d, 1 H, J = 2 Hz), 4.36 (d, 1 H, J = 2 Hz), 3.82 (m, 2 H), 3.53 (dxt, 1 H, J = 5, 15 Hz), 3.09 (dxt, 1 H, J = 5, 15 Hz), 2.91 (t, 1 H, J = 6 Hz (exchanges with D_2O); IR (KBr) 3422 (−OH), 2929, 1763 (C=O); EI MS, *m/z* 331 (M^+, $C_{17}H_{17}NO_4S$). Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23. Found: C, 61.32; H, 5.29; N, 4.25.

For Ester 22: ^{1}H NMR ($CDCl_3$) δ 8.61 (br s, 3 H), 8.01 (s, 1 H), 7.95 (d, 2 H, J = 8 Hz), 7.61 (t, 1 H, J = 7.5 Hz), 7.52 (m, 5 H), 7.39 (m, 3 H), 3.68 (t, 2 H, J = 5 Hz), 3.39 (quintet, 2 H, J = 5 Hz); IR (KBr) 1751 cm^{-1}; FAB MS, *m/z* 332 (M^+, $C_{17}H_{18}NO_4S$).

For 27: ^{1}H NMR ($CDCl_3$) δ 7.95 (dxd, 2 H, J = 2, 7 Hz), 7.82 (s, 1 H), 7.55 (m, 5 H), 7.37 (m, 3 H), 2.63 (s, 6 H); IR (KBr) 1702 cm^{-1}; EI MS, *m/z* 330.1051 (calcd for $C_{17}H_{18}N_2O_3S$ 330.1038).

Preparation of Sulfonate Salts 28. Tetra-*n*-butylammonium *trans*-4-Phenyl-3-(phenylsulfonyl)-2-azetidinone-1-sulfonate (28a). A solution of azetidinone **12a** (162 mg, 0.56 mmol) in pyridine (1 mL) was heated, under argon, to 80 °C, and the pyridine−sulfur trioxide complex (192 mg, 1.69 mmol) was added. The mixture, which quickly became homogeneous, was stirred overnight and then poured into 100 mL of 10% hydrochloric acid. The resulting solution was extracted with hexanes (2 × 25 mL), and the combined organic extracts were backwashed with an additional 25 mL of 10% hydrochloric acid solution. The combined aqueous layers were then treated with excess tetrabutylammonium hydrosulfate. The resulting mixture was extracted with CH_2Cl_2 (1 × 50 and 2 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to yield **28a** (320 mg, 83%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 8.01 (dxd, 2 H, J = 2, 8 Hz), 7.65 (t, 1 H, J = 8 Hz), 7.52 (t, 2 H, J = 8 Hz), 7.33 (m, 3 H), 7.20 (m, 3 H), 5.27 (d, 1 H, J = 2.5 Hz), 4.14 (d, 1 H, J = 2.5 Hz), 3.15 (m, 8 H), 1.55 (m, 8 H), 1.40 (sextet, 8 H, J = 7 Hz), 0.93 (t, 12 H, J = 7 Hz); IR ($CHCl_3$) 2960, 2877, 2330, 1768, 1281 cm^{-1}.

Tetra-*n*-butylammonium *trans*-4-Phenyl-3-(4-methylphenylsulfonyl)-2-azetidinone-1-sulfonate (28c). Azetidinone **12c** (0.602 g, 2.00 mmol) was treated as described to give **28c** as a colorless foam in 85% yield: ^{1}H NMR ($CDCl_3$) δ 7.84 (dxd, 2 H, J = 2, 8 Hz), 7.35 (m, 3 H), 7.25 (d, 2 H, J = 8 Hz), 7.21 (d, 2 H, J = 8 Hz), 5.30 (d, 1 H, J = 2.8 Hz), 4.15 (d, 1 H, J = 2.8 Hz), 3.22 (m, 8 H), 2.42 (s, 3 H), 1.58 (m, 8 H), 1.45 (sextet, 8 H, J = 7 Hz), 0.97 (t, 12 H, J = 7 Hz); IR ($CHCl_3$) 2960, 2875, 2330, 1775, 1259 cm^{-1}.

Reduction of *N*-Benzyl Azetidinone 14 Under Birch-Reduction Conditions. Azetidinone **14** (0.189 g, 0.500 mmol) was dissolved in 3 mL of dry THF. The resulting solution was added to 10 mL of liquid ammonia cooled to −78 °C. Sodium metal (0.023 g, 1.0 mg atom) was added in small pieces to the reaction mixture. After the addition was complete, the reaction mixture was stirred for 0.5 h at −78 °C. Solid NH_4Cl was added (0.20 g), and the cooling bath was removed. The ammonia was allowed to evaporate. The reaction mixture was partitioned between ether (25 mL) and water (25 mL). The organic phase was dried over $MgSO_4$ and concentrated. 3-Phenylpropionamide was the only observed product by ^{1}H NMR in addition to unreacted azetidinone **14**.

Ceric Ammonium Nitrate Oxidation of Azetidinone 15. A solution of azetidinone **15** (0.100 g, 0.25 mmol) and cerium ammonium nitrate (548 mg, 1 mmol) in CH_3CN (3 mL) and water (1 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Chromatography on SiO_2 eluted with 1:1 hexanes−EtOAc, gave 0.050 g (70%) of *trans*-**12a**.

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Supporting Information Available: An experimental section for X-ray structural determination of **16a** and tables of a Summary of Crystallographic Data for **16a**, Atomic Coordinates and Equivalent Isotropic Displacement Parameters, Bond Lengths and Angles, Anisotropic Displacement Parameters, and Hydrogen Coordinates. ^{1}H NMR spectra as well for α-phenylsulfonyl acetophenone, the crude reaction mixture for formation of **16a** and **16b** and **17**, and the crude reaction mixture for the formation of **22** and **23**, **23**, **27**, **28a**, and **28c** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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