dissolved in ethanolic sodium ethoxide [prepared by dissolving Na (0.06 g) in 30 mL of absolute EtOH]. The mixture was heated at reflux for 3 h. The solvent was removed by evaporation in vacuo, and the residue was dissolved in cold water. The resulting precipitate was collected by filtration to give 0.115 g of 7,[15] mp 58–60 °C. Recrystallization from petroleum ether gave pure 7: mp 65–67 °C; mass spectrum, m/e 209 (M^+); UV λ_{max} 322, 256, 234 (ϵ 3000, 11300, 34900).

Ethyl 5-Cyano-6-hydroxynicotinate (8). (a) A mixture of 1 (0.504 g, 0.003 mol) and cyanoacetamide (0.84 g, 0.01 mol) in ethanolic sodium ethoxide [prepared by dissolving Na (0.23 g, 0.01 mol) in 40 mL of absolute EtOH] was heated at reflux for 1 h. The solvent was removed in vacuo, and the residue was dissolved in cold water (20 mL). Upon acidification with concentrated HCl, the crystalline product precipitated and was collected by filtration: 0.233 g (46%);[15] mp 218–221 °C. Recrystallization from water gave analytically pure 8: mp 223–225 °C; NMR (Me_2SO-d_6) δ 1.30 (3 H, t, J = 7, CH_3), 4.24 (2 H, q, J = 7, CH_2), 8.29 (1 H, d, J = 2, C_6H), 8.42 (1 H, d, J = 2, C_4H), 13.08 (1 H, br, OH); mass spectrum, m/e 192 (M^+); UV λ_{max} 332, 261, 218 (sh), (ϵ 7200, 15100, 14000). Anal. Calcd for $C_9H_8O_3N_2$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.26; H, 4.16; N, 14.79.

(b) A solution of 9 (0.702 g, 0.003 mol) in ethanolic sodium ethoxide [prepared by dissolving Na (0.138 g, 0.006 mol) in 40 mL of absolute EtOH] was heated at reflux for 3.5 h. The reaction solution was evaporated to dryness, and the residue was dissolved in cold water (20 mL). The solution was acidified with concentrated HCl to give 8: 0.445 g (77%); mp 220–222 °C. The IR spectrum was identical with that of the compound prepared above.

5-(2-Carbamoyl-2-cyanovinyl)-1,3-dimethyluracil (9). A mixture of 1 (1.68 g, 0.01 mol), cyanoacetamide (1.01 g, 0.012 mol), piperidine (1 drop), and acetic acid (1 drop) was refluxed in 80 mL of benzene with separation of water as a benzene azeotrope for 2 h. The reaction mixture was evaporated to dryness. The residue was triturated with ether, and the resulting precipitate was collected by filtration to give 2.19 g (94%) of 9, mp 244–246 °C. Recrystallization from water gave analytically pure 9: 1.26 g (54%); mp 256–257 °C; NMR (Me_2SO-d_6) 3.23 (3 H, s, CH_3), 3.44 (3 H, s, CH_3), 8.05 (1 H, s, CH=C), 8.63 (1 H, s, C_6H); mass spectrum, m/e 234 (M^+); UV λ_{max} 344, 265, 234 (ϵ 16700, 7500, 5800). Anal. Calcd for $C_{10}H_{10}O_3N_4$: C, 51.28; H, 4.30; N, 23.92. Found: C, 50.98; H, 4.18; N, 23.71.

6-Acetyl-1,3,7-trimethylquinazoline-2,4(1*H*,3*H*)-dione (12). A mixture of 10 (0.546 g, 0.003 mol), acetylacetone (0.360 g, 0.0036 mol), piperidine (1 drop), and acetic acid (1 drop) in 80 mL of benzene was refluxed with separating water as a benzene azeotrope for 12 h. The reaction mixture was evaporated to dryness. The residue was triturated with ether, and the resulting precipitate was collected by filtration and recrystallized from ethanol to give 0.340 g (46%) of 12: mp 210–211 °C; NMR ($CDCl_3$) δ 2.67 (3 H, s, $COCH_3$), 2.70 (3 H, s, C_7CH_3), 3.49 (3 H, s, NCH_3), 3.62 (3 H, s, NCH_3), 7.04 (1 H, s, C_8H), 8.62 (1 H, s, C_5H); UV λ_{max} 284, 241 (ϵ 15200, 42300); mass spectrum, m/e 246 (M^+), 231 ($M^+ - 15$). Anal. Calcd for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.28; H, 5.80; N, 11.13.

Registry No. 1, 4869-46-9; **4a**, 57009-53-7; **4b**, 57009-12-8; **4c**, 74442-95-8; **4d**, 5985-25-1; **4e**, 74442-97-0; **4f**, 36727-23-8; **4g**, 74442-96-9; **5a**, 74442-98-1; **5b**, 78515-04-5; **6**, 78515-05-6; **7**, 78515-06-7; **8**, 74443-00-8; **9**, 74442-99-2; **10**, 23941-84-6; **12**, 78515-07-8; acetylacetone, 123-54-6; 1,3-dimethylurea, 96-31-1; acetoacetamide, 5977-14-0; ethyl acetoacetate, 141-97-9; dimethyl acetonedicarboxylate, 1830-54-2; phenylacetone, 103-79-7; malononitrile, 109-77-3; 1,3-dimethyluracil, 874-14-6; cyanoacetamide, 107-91-5.

Neber Rearrangement of Amidoximesulfonates. Synthesis of 2-Amino-1-azirines

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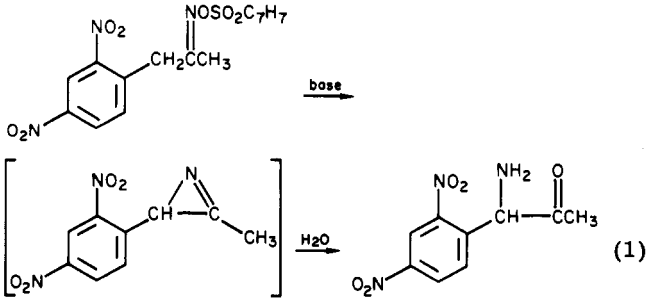
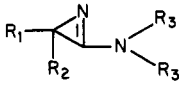
Amidoximes prepared from α-cyanoacetanilides and (phenylsulfonyl)acetonitrile were converted to the corresponding *O*-tosyl derivatives. Upon treatment with base, these amidoxime-*O*-sulfonates afforded 2-amino-1-azirines instead of the expected 3-amino-2-pyrazolin-5-ones. This transformation can be viewed as a new variant of the Neber rearrangement. Azirines bearing unsubstituted amino groups have not been reported previously; structure proof and reactions of these compounds are discussed.

Introduction

The Neber rearrangement of ketoxime-*O*-sulfonates to amino ketones, shown in its classic form in eq 1, proceeds via 1-azirine intermediates but has not been a generally useful preparation method for 1-azirines.[1,2] Other routes to 1-azirines are available,[3] however, and in recent years syntheses of 2-(*N*,*N*-dialkylamino)-1-azirines have been reported.[4,5] A considerable body of work, principally by Ghosez[6] and by Heimgartner[7] and their co-workers, has demonstrated that compounds of the type 1 are remarkably useful intermediates for the synthesis of a large array of heterocyclic compounds.



(1)

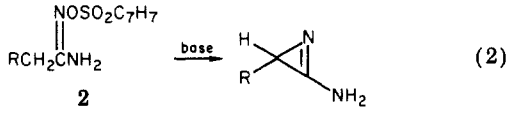


1, R_1 = H or alkyl or aryl; R_2 = alkyl or aryl; R_3 = alkyl

(1) O'Brien, C. *Chem. Rev.* **1964**, *64*, 81.
(2) Hassner, A.; Fowler, F. *J. Am. Chem. Soc.* **1968**, *90*, 2869.
(3) F. Fowler In "Advances in Heterocyclic Chemistry"; Academic Press: New York, 1971; Vol. 13, p 45.
(4) Rens, M.; Ghosez, L. *Tetrahedron Lett.* **1970**, 3765.
(5) de Voghel, G.; Eggerichs, T.; Clamot, B.; Viehe, H. *Chimia* **1976**, *30*, 191.
(6) Demoulin, A.; Gorissen, H.; Hesbain-Frisque, A. M.; Ghosez, L. *J. Am. Chem. Soc.* **1975**, *97*, 4409.
(7) For leading references, see Heimgartner, H. *Chimia* **1979**, *33*, 111.

0022-3263/81/1946-3953$01.25/0

We have recently examined the reaction of certain amidoxime *O*-tosylates **2** with base. The reaction shown in eq 2 gives high yields of azirines **1a** which bear a free amino group at position 2. This reaction is a new application of the Neber rearrangement and provides access to 2-amino-1-azirines which have not been obtained via the previously reported routes.

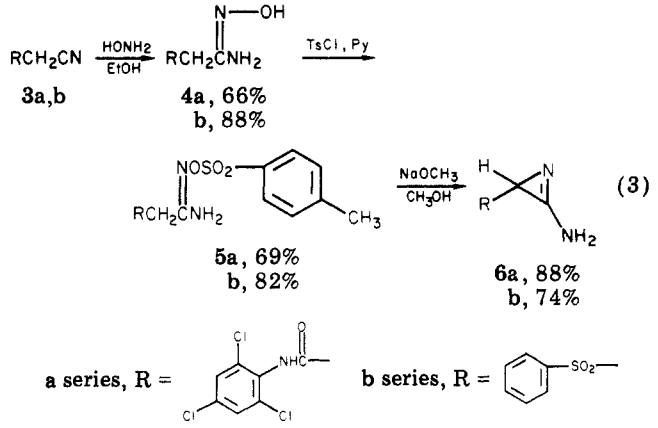


2 **1a** (2)

R = ArNHCO or $ArSO_2$

Results and Discussion

Equation 3 shows the conversion of 2-cyano-2′,4′,6′-trichloroacetanilide **3a** to amidoxime **4a**. Tosylation of **4a** gave amidoxime *O*-tosylate **5a**, which upon reaction with sodium methoxide in methanol gave 2-amino-1-azirine **6a** as the sole product. The formation of **6a** was somewhat

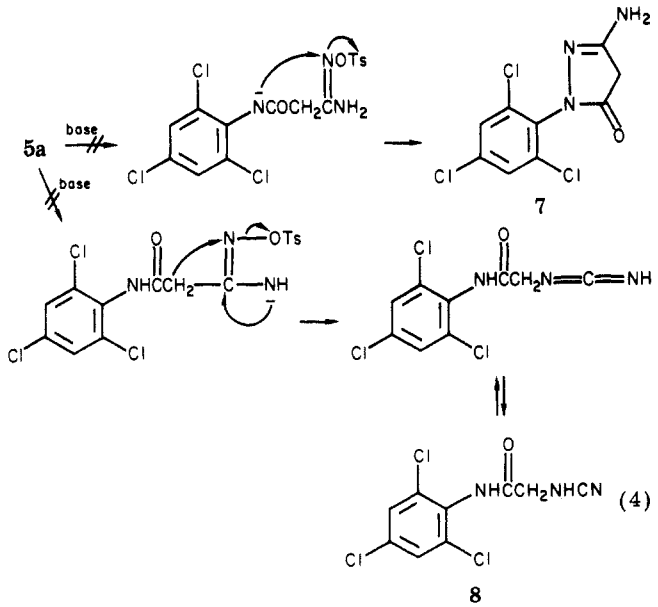


3a,b **4a**, 66% b, 88%

5a, 69% b, 82% **6a**, 88% b, 74% (3)

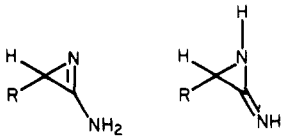
a series, R = b series, R =

surprising in view of the possibilities offered by **5a** for other reactions. Thus no traces of pyrazolone **7** or cyanamide **8** were detected in the reaction mixture (eq 4).



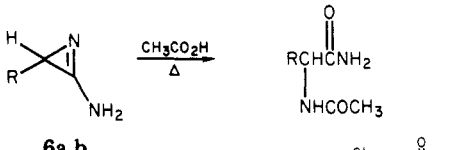
(4)

The structure assigned to **6a** is supported by both physical and chemical evidence. Compound **6a** has molecular weight 277 (mass spectrum) and displays C=N stretch in the infrared as a split band at 5.45 and 5.50 μm.[2-5] In addition to the expected aryl and NH_2 signals, the ^1H NMR spectrum of **6a** displays a one-proton singlet (δ 2.73) attributable to the azirine C_3-H. ^{13}C NMR analysis also supports structure **6a**. In addition to aryl and amide carbons, azirine C_2 is at 148.9 ppm; azirine C_3 bears a single proton (J_{13C-H} = 200 Hz).[8] These physical data are consistent with the existence of either tautomer, a or b, in **6a** or with an equilibrium mixture of both; form a is drawn merely as a convention.[9]

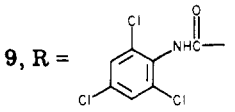


a b

Compound **6a** upon treatment with acetic acid afforded tris(amide) **9** in good yield. This type of ring opening has been seen before in 2-(*N*,*N*-dialkylamino)-1-azirines[10] and serves as good chemical evidence for structure **6a**. Upon

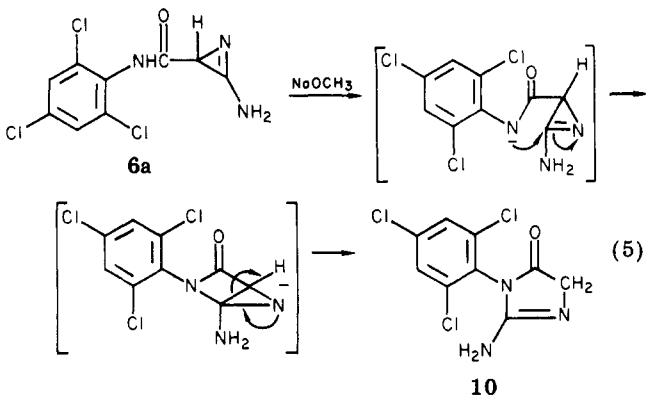


6a,b



11, R = $C_6H_5SO_2$-

treatment with excess sodium methoxide in methanol, **6a** underwent a novel rearrangement to give a single product for which we propose the 2-amino-5-imidazolone structure **10**. The structure **10** is assigned from the physical data [see the Experimental Section; in particular, the presence of $ArNC(NH_2)$=N (IR, NMR) and CH_2 groups (^1H and ^{13}C NMR)] and chemical evidence (base hydrolysis to 2,4,6-trichloroaniline[11]). Several mechanisms can be drawn to account for this transformation. The bicyclo[2.1.0] intermediate (eq 5) appears reasonable, since other



10 (5)

mechanisms (for instance, "vinylcyclopropane-like" ring expansion, or opening of the C_2–C_3 bond to give a 1,3-dipolar intermediate followed by closure to **10**) do not a priori require the presence of base. Compound **6a** did not rearrange or react with 1,3-dipolarophiles upon heating in neutral solution. Nevertheless, the mechanism in eq 5 has not yet been rigorously proven.

To demonstrate that this Neber route to 2-amino-1-azirines is not limited to amides of the type **6a**, the se-

(8) For ^{13}C NMR spectra of other 1-arizines, see Isomura, K.; Taniguchi, H; Mishima, M.; Fujio, M.; Tsuno, Y. *Org. Magn. Reson.* **1977**, *9*, 559.

(9) For characterization of an *N*,*N*′-dialkylaziridine imine, see Quast, H.; Schmitt, E. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 381.

(10) Vittorelli, P.; Heimgartner, H.; Schmid, H.; Hoet, P.; Ghosez, L. *Tetrahedron* **1974**, *30*, 3737.

quence **3b** through **6b** (eq 3) was carried out. Aminoazirine **6b**, like **6a**, was a stable solid with physical and chemical properties in accord with the proposed structure (see the Experimental Section for spectral data; conversion of **6b** to **11** for chemical evidence). Unlike **6a**, azirine **6b** did not give rise to a rearrangement product upon base treatment; decomposition to afford a mixture of unidentified, water-soluble degradation products occurred instead.

This route to 1-azirines appears limited to acetamidoximes bearing strongly electronegative α-substituents (COR, SO_2R); an attempted synthesis of **6** from **3** (R = C_6H_5) failed to produce azirine in the final step.

Conclusion

In summary, the chemistry presented here describes a new variant of the Neber rearrangement which affords, in straightforward operations and in preparatively useful yields, certain 2-(unsubstituted amino)-1-azirines which were heretofore inaccessible, and which may have considerable value in heterocyclic synthesis.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 instrument; ^1H NMR spectra were obtained with Varian EM-360 and JEOLCO MH-100 spectrometers; chemical shifts are reported relative to internal Me_4Si. ^{13}C NMR spectra were obtained on a Bruker 90 instrument; mass spectra were taken with Consolidated Electrodynamics Corporation Model 21-110B (electron impact) or Varian MAT 731 systems (field desorption).

Amidoxime 4a from Nitrile 3a. Hydroxylamine hydrochloride (1.7 g, 0.025 mol) was added to a stirred mixture of 2.7 g (0.025 mol) of sodium carbonate and 10 mL of 50% aqueous EtOH. This mixture was diluted with 100 mL of EtOH, and 5.28 g (0.020 mol) of nitrile **3a**[12] was added. The mixture was stirred at reflux for 1 h, cooled, and poured into 1 L of ice water. Filtration gave 3.9 g (66%) of **4a** as a tan powder. An analytical sample was recrystallized from EtOH: mp 200 °C; IR (KBr) 2.85, 2.94, 6.00, 6.60, 8.48, 10.28, and 11.62 μm; ^1H NMR (Me_2SO-d_6) δ 9.2 (br s, 1 H), 7.41 (s, 2 H), 5.28 (br s, 2 H), 3.20 (s, 2 H).

Anal. Calcd for $C_9H_8Cl_3N_3O_2$: C, 36.40; H, 2.71; N, 14.17. Found: C, 36.29; H, 2.84; N, 13.86.

Tosylate 5a from Amidoxime 4a. A solution of 7.2 g (0.024 mol) of amidoxime **4a** in 35 mL of pyridine was cooled to 0 °C and treated with 5.0 g (0.026 mol) of tosyl chloride. After 1 h at 0–5 °C, the mixture was added to ice water and filtered to give 7.5 g (69%) of tosylate **5a** as a white solid. An analytical sample from EtOH had a melting point at 151–152 °C: IR (KBr) 2.93, 3.10, 6.00, 6.09, 7.51, 8.57, and 12.2 μm; ^1H NMR (Me_2SO-d_6) δ 9.62 (br s, 1 H), 7.90 (d, J = 9, 2 H), 7.49 (s, 2 H), 7.33 (d, J = 9, 2 H), 6.31 (br s, 2 H), 3.28 (s, 2 H), 2.36 (s, 3 H).

Anal. Calcd for $C_{16}H_{14}Cl_3N_3O_4S$: C, 42.63; H, 3.13; N, 9.32. Found: C, 42.96; H, 3.29; N, 9.51.

Aminoazirine 6a from Tosylate 5a. A slurry of 35.0 g (0.078 mol) of tosylate **5a** in 350 mL of MeOH was treated dropwise at 25 °C with a solution of 4.2 g (0.078 mol) of sodium methoxide in 25 mL of MeOH. TLC analysis (silica gel, 5% MeOH in $CHCl_3$) indicated complete reaction in 20 min. The initially white slurry gave a clear yellow solution midway through the addition; tan solid reappeared at the end of the reaction. The mixture was cooled to 0 °C and filtered, and the solid product was washed thoroughly with water and air-dried. The yield of **6a** was 18.9 g (88%). An analytical sample was recrystallized from MeOH: mp 148–150 °C; IR (KBr) 3.0–3.4, 5.45, 5.50, 6.10, 6.45, 6.67, 6.69, 7.37, 7.51, 7.95, 8.35, 10.15, 10.54, 11.71, 12.14, and 14.3 μm; ^1H NMR (Me_2SO-d_6) δ 9.43 (br s, 1 H), 7.59 (s, 2 H), 7.47 (br s, 2 H), 2.73 (s, 1 H); ^{13}C NMR (Me_2SO-d_6) 32.9 (azirine C_3), 128.4 (m-Ar), 132.0 (p-Ar), 132.6 (C_1-Ar), 134.5 (o-Ar), 148.9 (azirine C_2), 170.3 (amide carbonyl); mass spectrum (FD), m/e 277 (M^+), 195 (5%).

Anal. Calcd for $C_9H_6Cl_3N_3O$: C, 38.80; H, 2.17; N, 15.08. Found: C, 38.56; H, 2.29; N, 15.28.

Base-Catalyzed Rearrangement of Azirine 6a to 10. A stirred mixture of 1.5 g (0.0054 mol) of aminoazirine **6a**, 30 mL of MeOH, and 0.5 g (0.0092 mol) of sodium methoxide was refluxed for 10 min. TLC analysis (silica gel, 10% MeOH in $CHCl_3$) showed loss of **6a** and formation of a single, more polar product. The reaction mixture was stripped in vacuo, and the resultant orange solid residue was dissolved in 10 mL of water and neutralized with acetic acid. The precipitated product was filtered to give 1.07 g (71%) of **10** as a white solid: mp (MeOH) 242–244 °C, IR (mull) 3.1–3.9, 5.92, 6.15, 8.21, 9.60, 11.4, 12.14 μm; ^1H NMR (Me_2SO-d_6) δ 7.33 (s, 2 H), 5.0 (br s, 2 H), 3.89 (s, 2 H); ^{13}C NMR (Me_2SO-d_6) 47.8 (C_4 of imidazole), 125.9 (p -Ar), 127.7 (m-Ar), 127.6 (C_1-Ar), 129.0 (σ-Ar), 152.1 (C_2 of imidazole), 173.5 (C_5 of imidazole); mass spectrum, m/e 277 (M^+), 220 (100%).

Anal. Calcd for $C_9H_6Cl_3N_3O$: C, 38.80; H, 2.17; N, 15.08. Found: C, 38.78; H, 2.37; N, 15.29.

Malondiamide 9 from Aminoazirine 6a. A mixture of 1.0 g (0.0036 mol) of azirine **6a** and 40 mL of glacial HOAc was warmed at about 50 °C for 1 h and cooled to 25 °C, and the resulting crystals were filtered, washed with ethanol, and air-dried to give 0.80 g (66%) of amide **9**: mp 262–263 °C (EtOH); IR (KBr) 3.0, 5.93, 6.09, 6.62, 7.31, 8.75, 11.61, 12.4 μm; ^1H NMR (CF_3CO_2H) δ 9.0 (br s, 1 H, exchangeable with D_2O), 8.20 (d, J = 6, 1 H, D_2O exchangeable), 7.60 (br s, 2 H, exchangeable with D_2O), 7.57 (s, 2 H), 5.52 (d, J = 6, 1 H; collapses to s on D_2O addition), 2.43 (s, 3 H); mass spectrum, m/e 337 (M^+).

Anal. Calcd for $C_{11}H_{10}Cl_3N_3O_3$: C, 39.01; H, 3.19; N, 12.41. Found: C, 39.18; H, 3.07; N, 12.37.

(Phenylsulfonyl)acetamidoxime (4b). (Phenylsulfonyl)-acetamidoxime (**4b**) was prepared from (phenylsulfonyl)acetonitrile in 88% yield, according to the published procedure.[13]

Amidoxime Tosylate 5b. Amidoxime **4b** was tosylated by the same procedure used for compound **5a** (82% yield). The product had a melting point at 177–179 °C; IR (KBr) 2.95, 3.02, 6.10, 7.52, 8.60, 11.60, 12.10, and 12.29 μm; ^1H NMR (Me_2SO-d_6) δ 8–7.3 (m, 9 H), 6.70 (br s, 2 H, D_2O exchangeable), 4.00 (s, 2 H), 2.40 (s, 3 H).

Anal. Calcd for $C_{15}H_{16}N_2O_5S_2$: C, 48.89; H, 4.37; N, 7.60. Found: C, 48.97; H, 4.48; N, 7.70.

2-Amino-3-(phenylsulfonyl)-1-azirine (6b). A mixture of 30 g (0.082 mol) of tosylate **5b** and 250 mL of MeOH was stirred at 25 °C during addition (30 min) of 4.54 g (0.082 mol) of sodium methoxide in 50 mL of MeOH. The mixture was stripped of MeOH and partitioned between water and EtOAc. The organic phase was dried and stripped in vacuo to give an orange syrup which crystallized when scratched. The resulting solid was triturated with toluene, filtered, and air-dried to give 12.0 g (74%) of azirine **6b** as a tan solid: mp 106–107 °C (toluene–$CHCl_3$); IR (KBr) 2.91, 3.02, 5.47, 5.51, 6.96, 7.6–7.8, 8.7–8.8, 9.27, 10.50, 13.17, 14.08, and 14.60 μm; ^1H NMR ($CDCl_3$) δ 8.2–7.5 (m, 5 H), 6.70 (br s, 2 H), 3.68 (s, 1 H); ^{13}C NMR ($CDCl_3$) 50.2 (C_3 of azirine), 127.6 (σ-Ar), 129.2 (m-Ar), 133.5 (p-Ar), 139.0 (C_1 of Ar), 149.0 (C_2 of azirine); mass spectrum (FD), m/e 196 (M^+), 141 (100%).

Anal. Calcd for $C_8H_6N_2O_2S$: C, 48.97; H, 4.10; N, 14.28. Found: C, 48.82; H, 4.14; N, 14.33.

Amide 11 from Azirine 6b. A mixture of 1.0 g (0.0051 mol) of **6b** and 10 mL of HOAc was warmed at 50–70 °C for 0.5 h and cooled to 25 °C. The crystalline product was filtered, washed with EtOH, and air-dried to give 0.94 g (72%) of amide **11**: mp 162–163 °C (EtOH); IR (KBr) 2.9–3.1, 5.9, 6.0, 7.7, 8.78, 9.3, 13.7, and 14.55 μm. ^1H NMR (Me_2SO-d_6) δ 8.90 (d, J = 9, 1 H, D_2O exchangeable), 8.1–7.6 (m, 5 H), 7.50 (br s, 2 H, D_2O exchangeable), 6.08 (d, J = 9, 1 H, collapses to s on D_2O addition), 1.74 (s, 3 H).

Anal. Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.87; H, 4.68. Found: C, 46.71; H, 5.02.

Acknowledgment. The author is grateful to A. T. Spaugh for collection and analysis of the ^{13}C NMR spectra.

Registry No. 3a, 24522-44-9; **4a**, 78515-46-5; **4b**, 17665-60-0; **5a**, 78515-47-6; **5b**, 78515-48-7; **6a**, 78515-49-8; **6b**, 78515-50-1; **9**, 78515-51-2; **10**, 78515-52-3; **11**, 78515-53-4; hydroxylamine·HCl, 5470-11-1; tosyl chloride, 98-59-9.

(11) When **10** was refluxed in 20% aqueous NaOH, 2,4,6-trichloroaniline was the sole organic-soluble product formed (78% yield).

(12) Seidel, M.; Viste, K.; Yih, R. *Ger. Offen.* 1900947, 1969, to Rohm and Haas Co.; *Chem. Abstr.* **1970**, *72*, 21616g.

(13) Santilli, A.; Morris, R. *J. Heterocycl. Chem.* **1979**, *16*, 1197.