α-Lactam Intermediates in Base-Promoted Reactions of O-Sulfonylated Hydroxamic Acids with Nucleophiles†

Robert V. Hoffman,* Naresh K. Nayyar, and Wenting Chen

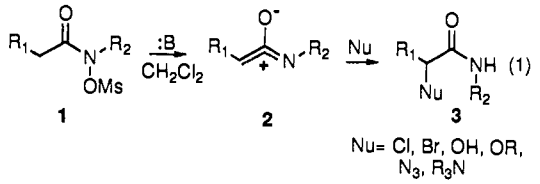
Contribution from the Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, New Mexico 88003-0001

Received February 1, 1993

Abstract: The reaction of *N*-(sulfonyloxy) amides with bases proceeds by initial formation of an α-lactam intermediate. A primary kinetic deuterium isotope effect, k_H/k_D = 2.17, a leaving group effect, $\beta_{lg}^{CH_3}$ = 0.50, and nucleophilic trapping all confirm that the α-lactam is produced in the rate-determining step. Ring opening to an ion pair and nucleophilic addition to C-2 produce 2-substituted amide products.

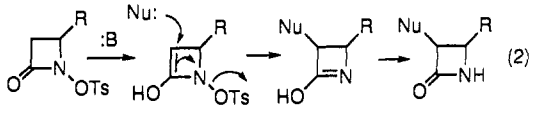
Introduction

Recently it was reported that O-sulfonylated hydroxamic acids **1** undergo base-promoted conversion to a variety of 2-substituted secondary amides **3** (eq 1).[1] We suggested that rate-determining removal of the α-proton by base followed by loss of the leaving group gives ion pair **2** which is captured by added nucleophiles to give 2-substituted products **3**.[1,2] Involvement of ion pair **2** in the product-forming step was strongly suggested because even poor nucleophiles (Cl^-, MsO^-, etc.) were incorporated efficiently at the α-position of the product under appropriate conditions. One requirement for the success of this transformation is that a conjugating group, either aryl or vinyl, be present at C-2, presumably to acidify C-2 protons for removal by base.



1 2 3 (1)

This scenario contrasts with the report of Miller[3] who suggested that a comparable transformation of *N*-(sulfonyloxy) β-lactams proceeds by S_N2' attack by nucleophiles at the α-position of enol derivatives of the *N*-(sulfonyloxy) β-lactam (eq 2). Adding to the mechanistic complexity is the report that *N*-(tosyloxy) derivatives of δ-lactams fail to produce α-substituted products whereas γ-lactams give 3-(tosyloxy) γ-lactams upon treatment with DBU but not other bases.[4]

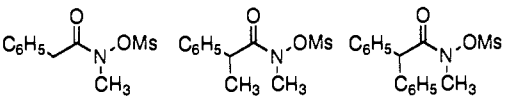


(2)

The present study of acyclic *N*-(sulfonyloxy) amides was undertaken in order to (a) examine structural effects on the reaction outcome in the framework of a proposed mechanism, (b) confirm that proton removal by base is irreversible and rate-determining, and (c) define the effect of a leaving group on the reaction rate. The results reveal that the mechanism of the reaction of acyclic *N*-(mesyloxy) amides with bases involves the initial conversion of **1** to an α-lactam intermediate which undergoes subsequent transformation to ion pair **2**. Conversion to product takes place by reaction of nucleophiles with either α-lactam or the ion pair.

Results and Discussion

Our initial studies of base-promoted reactions of *N*-(sulfonyloxy) amide derivatives utilized phenylacetic acid derivatives.[1] As more systems were examined, however, it became clear that formation of ion pair **2** was more complex than a simple two-step process, proton removal followed by loss of leaving group, that was initially envisioned. For example, *N*-(mesyloxy) phenyl amide **4** reacts smoothly with several base/nucleophile combinations,[1b] but α-methyl analog **5** and diphenyl analog **6** fail to react under the same conditions. Furthermore, neither **5** nor **6** with triethylamine and D_2O gave hydrogen–deuterium exchange at the 2-position under the reaction conditions. Proton removal from the α-position of **5** might be slower than for unsubstituted **4** due to the inductive effect of the α-methyl group, but it certainly should not be curtailed completely. On the other hand, mesyloxy compound **6** was expected to react *faster* than **4**, since proton removal should be facilitated by the additional conjugation. The observation that neither **5** nor **6** produces 2-substituted products is not consistent with simple proton removal being the rate-determining step.



4 5 6

To reaffirm that α-proton removal is involved in the rate-determining step, the reactions of **4** and **4**-α,α-d_2 with triethylamine (2.0 equiv) were followed by ^1H NMR. Second-order rate constants obtained for the two substrates, (6.00 ± 0.42) × 10^{-3} L mol^{-1} s^{-1} and (2.76 ± 0.15) × 10^{-3} L mol^{-1} s^{-1}, respectively, at 23 °C, give a primary kinetic deuterium isotope effect of k_H/k_D = 2.17. Thus, α-proton removal by base is involved in the rate-determining step.

Next, the reversibility of proton removal was reexamined. It was reported that treatment of **4** with triethylamine in D_2O failed to give deuterium incorporation at the α-position.[1a] As it is much easier to observe incorporation of hydrogen into a deuterated starting material, **4**-α,α-d_2 was treated with triethylamine, trimethylammonium chloride, and water. After partial reaction,

† This paper is dedicated to Prof. Harold Shechter of The Ohio State University on the occasion of his 70th birthday.

(1) (a) Hoffman, R. V.; Nayyar, N. K.; Klinekole, B. W. *J. Am. Chem. Soc.* **1992**, *114*, 6262. (b) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1992**, *57*, 5700.

(2) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1993**, *58*, 2355.

(3) (a) Gasparski, C. M.; Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 2741. (b) Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 548. We thank Prof. Miller for a preprint of this paper.

(4) Biswas, A.; Miller, M. J. *Heterocycles* **1987**, *26*, 2849.

0002-7863/93/1515-5031$04.00/0 © 1993 American Chemical Society

Table I. Second-Order Rate Constants for Reaction of *N*-((Arylsulfonyl))oxy Amides with Triethylamine in Chloroform-*d* at 25 °C

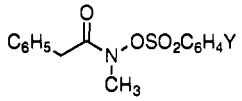
arenesulfonate	$[C_a]_0$[a]	$[C_b]_0$[b]	$k_2 \times 10^3$ (L mol^{-1} s^{-1})[c]
7a	0.195	0.391	1.03
7b	0.195	0.391	2.59
7c	0.294	0.388	6.91
7d	0.27	0.387	25.9

[a] Initial concentration (mol/L) of *N*-((arylsulfonyl)oxy) amide. [b] Initial concentration (mol/L) of triethylamine. [c] Rate constants are an average of replicate runs that vary ±7.5%.

reisolation of **4** showed that no hydrogen was incorporated at the α-position; thus, proton removal is rate-determining and irreversible.

Attention was turned to the role of the leaving group in the process. An inductive effect had been invoked to explain the greater rate of reaction when a triflate leaving group was used in place of the mesyloxy group of **4**.[1a] While the relative reactivities of triflate to mesylate were known only qualitatively, any significant rate influence by an inductive effect operating three bonds away from the site of proton removal was unsettling.

The influence of a leaving group on the reaction rate was evaluated quantitatively by preparing a series of *N*-(arenylsulfonyloxy)-*N*-methylphenylacetamides (**7a–d**) and following their rate of reaction with triethylamine by ^{1}H NMR. Good second-



7a Y=p-CH_3, **7b** Y=p-Br
7c Y=m-CF_3, **7d** Y=p-NO_2

order rate plots (>75% reaction) provided the rate constants in Table I. A Hammett plot of the rate data (log *k*) versus σ-values for arenesulfonate substituents gave $\rho = 1.4$ ($r = 0.99$). Since the ρ-value for acidity (pK_a) of arenesulfonic acids is $\rho = 0.61$,[5] a ρ-value for the inductive effect of arenesulfonate groups on the acidity of more distant protons should have $\rho < 0.61$. Therefore, the value of $\rho = 1.4$ is much too large to result from an inductive influence on the acidity of α-protons, but it is a typical value for a reaction in which an arenesulfonate group functions as a leaving group in the rate-determining step.[5]

A plot of the rate data (log *k*) versus pK_{lg} gave $\beta_{lg}^{Me} = 0.50$ ($r = 0.983$).[6] The transition-state parameter β_{lg}^{Me} is a Bronsted-type parameter which serves as a measure of the extent of bond cleavage to an arenesulfonate leaving group at the transition state. The magnitude of β_{lg}^{Me} is also indicative of the reaction mechanism. In ethanol solvent, nucleophilic displacements of arenesulfonate groups typically have β_{lg}^{Me} values centered around 0.44 whereas simple ionizations of an arenesulfonate leaving group have β_{lg}^{Me} values near 0.60. Reactions in which intramolecular electron donation aids leaving group departure typically have β_{lg}^{Me} values near 0.5.[6] In the present case, a β_{lg}^{Me} value of 0.50 is a typical value for reactions in which an arenesulfonate group functions as a leaving group from nitrogen in a base-promoted elimination reaction.[7]

These results convincingly argue that *both* proton removal by base and loss of leaving group are occurring at the transition state of the rate-determining step of the reaction. These mechanistic requirements suggest that the rate-determining step is either direct conversion of the starting O-sulfonated hydroxamate to ion pair **2** without involvement of the enolate or base-promoted 1,3-elimination to produce α-lactam **8** (Scheme I). These two

Scheme I

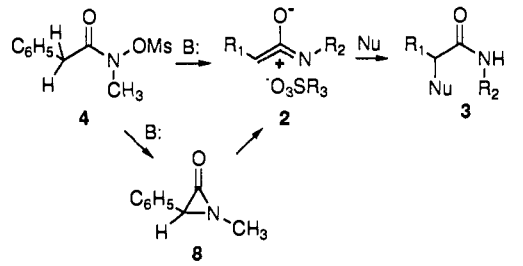
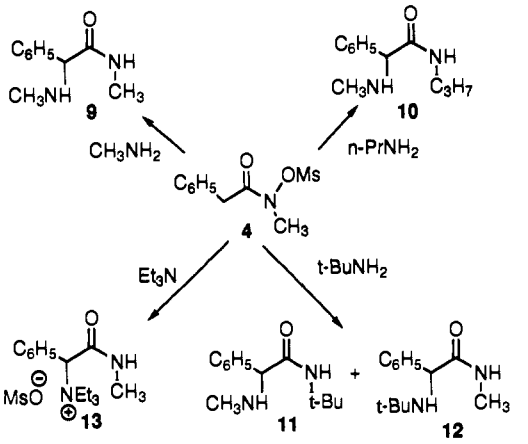


Chart I



processes are related since ion pair **2** and α-lactam **8** are valence tautomers. Of these two possibilities, α-lactam formation is more likely. α-Lactams are known to be discrete intermediates in base-promoted reactions of *N*-chloro amides[8] and 2-halo amides,[9] and one has reportedly been isolated from reaction of an *N*-(tosyloxy) amide with base.[10] Nucleophiles often react with α-lactams by addition to a carbonyl group. Without steric stabilization, however, α-lactams **8** rapidly undergo ring opening to ion pairs **2** and yield only 2-substituted products by addition of nucleophiles to C-2.[11]

The intermediacy of an α-lactam in base-promoted reactions of *N*-(sulfonyloxy) amide **4** was conclusively demonstrated by its interception with amine nucleophiles (Chart I). Reaction of **4** with methylamine (2.2 equiv) gave amino amide **9** in excellent yield. The two *N*-methyl groups of **9** had distinctive NMR signals that could be used to assign their positions. When the *N*-methyl group is an *N*-methyl amide group, it is split by the N–H proton and appears as a doublet at about δ 2.8 ($J \simeq 5$ Hz). When the *N*-methyl group is an *N*-methylamine group at C-2, it appears as a singlet at about δ 2.41. Reaction of **4** with *n*-propylamine (2.2 equiv) gave a single product which contained both *n*-propylamino and methylamino groups. The *N*-methyl signal (singlet, δ 2.44) indicated that the product is *N*-propyl amide **10**, and this assignment was confirmed by independent synthesis. Evidentally, *n*-propylamine is sufficiently nucleophilic to trap α-lactam intermediate **8** by attack at the carbonyl carbon of **8** to give **10**.

On the other hand, reaction of **4** with *tert*-butylamine gave an 80:20 mixture of **11** and **12**. The steric bulk of *tert*-butylamine decreases its nucleophilicity to the extent that ring opening of

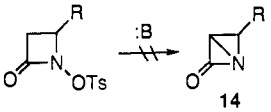
(5) Hoffman, R. V.; Belfoure, E. L. *J. Am. Chem. Soc.* **1982**, *104*, 2183.
(6) Hoffman, R. V.; Shankweiler, J. M. *J. Am. Chem. Soc.* **1986**, *108*, 5536.
(7) Hoffman, R. V.; Shankweiler, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 4019.

(8) (a) Baumgarten, H. E. *J. Am. Chem. Soc.* **1962**, *84*, 4975. (b) Baumgarten, H. E.; Zey, R. L.; Krolls, U. *J. Am. Chem. Soc.* **1961**, *83*, 4469.
(9) (a) Quast, H.; Leybach, H.; Wurthwein, E.-U. *Chem. Ber.* **1992**, *125*, 1249. (b) Quast, H.; Leybach, H. *Chem. Ber.* **1991**, *124*, 2105. (c) Scrimin, P.; D'Angeli, F.; Veronese, A. C. *Synthesis* **1982**, 586. (d) Baumgarten, H. E.; Fuerholtzer, J. J.; Clark, R. D.; Thompson, R. D. *J. Am. Chem. Soc.* **1963**, *85*, 3303. (e) Sheehan, J. C.; Frankenfeld, J. W. *J. Am. Chem. Soc.* **1961**, *83*, 4792. (f) Sheehan, J. C.; Lengyel, I. *J. Am. Chem. Soc.* **1964**, *86*, 1356.
(10) Bladon, C. M.; Kirby, G. W. *J. Chem. Soc., Chem. Commun.* **1982**, 1402.
(11) For an excellent review of α-lactam chemistry, see: Sheehan, J. C.; Lengyel, I. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 25.

α-lactam **8** to ion pair **2** and conversion to **12** competes with the direct trapping of **8** to give **11**. As expected, reaction of **4** with triethylamine, which has even lower nucleophilicity due to greater steric bulk, gives only 2-triethylammonium salt **13**.[1b] In this instance, nucleophilic attack on **8** by triethylamine is slower than its ring opening to ion pair **2**, so only the 2-substituted product is formed.

These results clearly show that reaction of *N*-(mesyloxy) amides **4** with bases proceeds by rate-determining, concerted 1,3-elimination to produce an α-lactam, **8** (Scheme I). With modest nucleophiles (Cl^-, Br^-, H_2O,[1b] N_3^-,[2] or Et_3N[1b]) and/or protic conditions, ring opening of **8** to ion pair **2** followed by nucleophilic capture at C-2 gives 2-substituted amide products **3**. More reactive amine nucleophiles successfully trap the α-lactam intermediate by addition to the carbonyl group of **8**. Amine nucleophilicity, however, can be moderated by steric effects to the extent that ring opening of **8** to an ion pair competes with carbonyl addition. The failure of both **5** and **6** to give products is consistent with this scenario as well, since α-lactam formation requires the close approach and formation of a bond between C-2 and the hydroxamate nitrogen. A second substituent at C-2 apparently produces a sufficiently large steric interaction with the alkyl substituent on nitrogen to prevent α-lactam formation.

This scenario also helps to explain the puzzling differences in results between acyclic hydroxamate systems, which we have studied, and data reported by Miller for base-promoted reactions of *N*-(tosyloxy) β-lactams.[3] In both systems, incorporation of nucleophiles at the α-position is observed; however, distinct reactivity differences are evident. For example, *N*-(tosyloxy) β-lactams react smoothly with trimethylsilyl azide and triethylamine to give α-azido β-lactams.[3b] However, *N*-(mesyloxy) amide **4** fails to give any 2-azido amide under similar conditions. Since we demonstrate here that α-lactam intermediates are produced initially in the reactions of acyclic *N*-(mesyloxy) amides and since a similar pathway in the β-lactam series would lead to a highly strained azabicyclobutanone, **14** (eq 3), it is very likely that different pathways are followed in these two systems. Miller has suggested that α-substitution reactions in a β-lactam series occur by S_N2' displacement on an enol derivative of *N*-(tosyloxy) β-lactam.[3a] This appears to be an excellent mechanistic alternative in the β-lactam series.



(3)

14

Experimental Section

Melting points were obtained on a Mel Temp apparatus and are uncorrected. Infrared spectral data (Perkin-Elmer 283) are reported in cm^{-1}. Chemical shifts for both proton NMR spectra (Varian XL-200) and ^{13}C NMR spectra (Varian Unity-400) are reported for chloroform-*d* solutions in ppm relative to Me_4Si. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Thin-layer chromatography was performed on silica gel 60 F254 plates from EM reagents, and the plates were visualized by UV irradiation or iodine vapor. Flash column chromatography was performed using silica gel 60 (230–400 mesh). *N*-Hydroxy-*N*-alkylacetanilides and *N*-sulfonyl-*N*-alkylacetanilides were prepared by literature methods[1] and purified by flash column chromatography (hexane:ethyl acetate, 6:4) or by crystallization (hexane:dichloromethane). Phenylacetic-α,α-d_2 acid (98 atom % D), diphenylacetyl chloride, diphenylacetic acid, and 2-phenylpropionic acid were purchased from Aldrich and used as received. α-Deuteriodiphenylacetic acid, which had 90% deuterium incorporation, was prepared according to a known procedure.[12]

General Procedure for Synthesis of *N*-Hydroxy-*N*-alkyl-2-arylacetamides. Oxalyl chloride (12 mmol) was added to a solution of the appropriate carboxylic acid (10 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. The solution was concentrated in vacuo, redissolved in CH_2Cl_2 (75 mL), and added dropwise to a 0 °C mixture of *N*-alkylhydroxylamine hydrochloride (12 mmol) and Et_3N (22 mmol) in CH_2Cl_2 (100 mL) over a period of 45–60 min. The mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with water (100 mL), and the organic layer was washed with 1 N HCl (2 × 25 mL) and brine (2 × 100 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by either recrystallization (benzene or hexane:CH_2Cl_2) or flash chromatography (hexane:ethyl acetate, 1:9).

General Procedure for the Preparation of *N*-(Sulfonyloxy)-*N*-alkyl-2-arylacetamides. Triethylamine (5 mmol) was added to a solution of *N*-hydroxy-2-aryl-*N*-alkylacetamide (5 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The mixture was stirred for 10–12 min, and a solution of sulfonyl chloride (5.5 mmol) in CH_2Cl_2 (25 mL) was added dropwise. After being stirred at 0 °C for 2 h, the solution was allowed to warm to room temperature and stirred for another 2 h. The organic layer was washed with water (2 × 20 mL), 1 N HCl (15 mL), and brine (20 mL) and dried over $MgSO_4$. After solvent removal by rotary evaporation, the product was usually purified by recrystallization (hexane:CH_2Cl_2) or flash chromatography (hexane:ethyl acetate, 6:4).

***N*-(((4-Methylphenyl)sulfonyl)oxy)-*N*-methylphenylacetamide (7a)** was prepared from *N*-hydroxy-*N*-methylphenylacetamide,[1b] 4-methylbenzenesulfonyl chloride, and triethylamine in 70% yield after recrystallization: mp 54–56 °C; ^1H NMR δ 2.49 (s, 3H, CH_3), 3.14 (s, 3H, NCH_3), 3.54 (s, 2H, $COCH_2$), 7.06 (d, J = 6.8 Hz, 2H, Ar*H*), 7.23–7.30 (m, 3H, Ar*H*), 7.42 (d, J = 8.4 Hz, 2H, Ar*H*), 7.91 (d, J = 8.4 Hz, 2H, Ar*H*); ^{13}C NMR δ 21.2, 38.4, 39.4, 127.0, 128.4, 129.4, 129.6, 130.3, 133.2, 146.9, 175.9; IR ($CHCl_3$) 3020, 1695, 1598, 1506, 1476, 1387, 1216, 1187, 1181, 1127, 1091, 1053 cm^{-1}.

***N*-(((4-Bromophenyl)sulfonyl)oxy)-*N*-methylphenylacetamide (7b)** was prepared from *N*-hydroxy-*N*-methylphenylacetamide,[1b] 4-bromobenzenesulfonyl chloride, and triethylamine in 75% yield after recrystallization: mp 84–86 °C; ^1H NMR δ 3.18 (s, 3H, NCH_3), 3.59 (s, 2H, $COCH_2$), 7.06 (d, J = 7.2 Hz, 2H, Ar*H*), 7.23–7.31 (m, 3H, Ar*H*), 7.76 (d, J = 8.8 Hz, 2H, Ar*H*), 7.87 (d, J = 8.4 Hz, 2H, Ar*H*); ^{13}C NMR δ 38.4, 39.6, 127.2, 128.5, 129.4, 130.7, 131.0, 132.9, 133.0, 176.0; IR ($CHCl_3$) 3030, 1702, 1575, 1497, 1472, 1455, 1394, 1280, 1196, 1114, 1089, 1070, 1012 cm^{-1}.

***N*-(((3-(Trifluoromethyl)phenyl)sulfonyl)oxy)-*N*-methylphenylacetamide (7c)** was prepared from *N*-hydroxy-*N*-methylphenylacetamide,[1b] 3-(trifluoromethyl)benzenesulfonyl chloride, and triethylamine in 73% yield after recrystallization: mp 85–86 °C; ^1H NMR δ 3.18 (s, 3H, NCH_3), 3.62 (s, 2H, $COCH_2$), 7.07 (d, J = 7.2 Hz, 2H, Ar*H*), 7.23–7.30 (m, 3H, Ar*H*), 7.76–7.80 (dd, J = 7.6 and 8.0 Hz, 1H, Ar*H*), 8.01 (d, J = 7.6 Hz, 1H, Ar*H*), 8.22 (d, J = 8.0 Hz, 1H, Ar*H*), 8.29 (br s, 1H, Ar*H*); ^{13}C NMR δ 39.1, 39.8, 126.3, 126.3, 126.4, 126.4, 127.3, 128.6, 129.4, 130.5, 131.8, 131.9, 131.9, 132.6, 132.8, 135.2, 175.4; IR ($CHCl_3$) 3033, 1708, 1611, 1498, 1456, 1436, 1392, 1327, 1196, 1137, 1073, 1001 cm^{-1}.

***N*-(((4-Nitrophenyl)sulfonyl)oxy)-*N*-methylphenylacetamide (7d)** was prepared from *N*-hydroxy-*N*-methylphenylacetamide,[1b] 4-nitrobenzenesulfonyl chloride, and triethylamine in 73% yield after recrystallization: mp 97–98 °C; ^1H NMR δ 3.27 (s, 3H, NCH_3), 3.62 (s, 2H, $COCH_2$), 7.04–7.08 (m, 2H, Ar*H*), 7.26–7.29 (m, 3H, Ar*H*), 8.18 (d, J = 8.9 Hz, 2H, Ar*H*), 8.38 (d, J = 8.9 Hz, 2H, Ar*H*); ^{13}C NMR δ 39.5, 39.8, 124.5, 127.4, 128.7, 129.1, 129.1, 129.2, 130.8, 132.6, 139.3, 151.4; IR ($CHCl_3$) 3020, 1705, 1608, 1538, 1497, 1456, 1407, 1399, 1350, 1313, 1216, 1196, 1089, 1015 cm^{-1}.

***N*-(Mesyloxy)-*N*-methyl-α,α-dideuteriophenylacetamide (4-α,α-d_2)** was prepared from phenylacetic acid-α,α-d_2 by conversion to the *N*-methyl hydroxamic acid followed by reaction of the crude hydroxamic acid with methanesulfonyl chloride and triethylamine (91% crude yield, 62% yield after crystallization): mp 69–70 °C; ^1H NMR δ 3.13 (s, 3H, O_2SCH_3), 3.44 (s, 3H, NCH_3), 7.22–7.35 (m, 5H, Ar*H*); ^{13}C NMR δ 37.6, 39.6, 127.4, 128.7, 129.2, 132.8, 173.5; IR ($CHCl_3$) 3031, 2938, 2254, 1697, 1605, 1498, 1450, 1375, 1328, 1186, 1135, 1078 cm^{-1}.

***N*-(Mesyloxy)-*N*-methyl-2-methylphenylacetamide (5)** was prepared from 2-phenylpropionic acid by conversion to the corresponding hydroxamic acid and reaction with methanesulfonyl chloride (80% yield, 79% yield after column chromatography): oil; ^1H NMR δ 1.47 (d, J = 6.9 Hz, 3H, $PhCHCH_3$), 3.06 (s, 3H, SCH_3), 3.36 (s, 3H, NCH_3), 4.00 (q, 1H, J = 6.9 Hz, $PhCHCH_3$), 7.24–7.34 (m, 5H, Ar*H*); ^{13}C NMR δ 19.9, 37.6, 39.8, 43.5, 127.4, 127.4, 129.1, 139.5, 175.8; IR (neat) 3031, 2983, 2937, 1699, 1602, 1494, 1455, 1376, 1270, 1186, 1119, 1070, 1048 cm^{-1}.

(12) Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M., Jr. *J. Org. Chem.* **1972**, *37*, 451.

N-(Mesyloxy)-N-methyl-2,2-diphenylacetamide (6) was prepared from diphenylacetic acid by conversion to the corresponding hydroxamic acid and reaction of the crude hydroxamic acid with methanesulfonyl chloride (83% crude yield, 76% after recrystallization): mp 97–98 °C; ^{1}H NMR δ 3.08 (s, 3H, SCH_3), 3.45 (s, 3H, NCH_3), 5.35 (s, 1H, Ph_2CH), 7.24–7.39 (m, 10H, ArH); ^{13}C NMR δ 37.8, 40.2, 54.3, 127.6, 128.8, 128.8, 137.5, 174.0; IR ($CHCl_3$) 3089, 3064, 3031, 2938, 1695, 1601, 1496, 1454, 1375, 1186, 1082, 1033 cm^{-1}.

N-(Mesyloxy)-N-methyl-α-deuterio-2,2-diphenylacetamide (6-α-*d*) was prepared from α-deuteriodiphenylacetic acid[12] via the corresponding crude hydroxamic acid (90% yield; ^{1}H NMR δ 3.21–3.33 (2 s, 3H, NCH_3), 5.09 (s, 0.1H, $CHPh_2$), 7.26–7.48 (s, 10H, ArH), 8.48 (br s, 1H, OH); IR ($CHCl_3$) 3260, 3020, 2956, 1621, 1491, 1453, 1427, 1398, 1216, 1110, 1080, 1040 cm^{-1}) in 70% yield after crystallization: mp 100–101 °C; ^{1}H NMR δ 3.08 (s, 3H, SCH_3), 3.45 (s, 3H, NCH_3), 5.35 (s, 0.25H, Ph_2CH), 7.24–7.40 (m, 10H, ArH); ^{13}C NMR δ 37.8, 40.1, 54.3, 127.5, 128.8, 128.8, 133.5, 174.0; IR ($CHCl_3$) 3028, 2937, 1697, 1600, 1496, 1451, 1374, 1186, 1082, 1033 cm^{-1}.

Rates of Reaction of N-(Sulfonyloxy) Amides 4, 4-α,α-d_2, and 7a–d with Triethylamine. An *N*-(sulfonyloxy) amide was weighed into an NMR tube and treated with a known volume of a 0.41 M solution of triethylamine in chloroform-*d* at 23 °C. The mixture was then placed in the thermostated probe of the NMR (23 ± 0.2 °C), and spectra were recorded at regular intervals. The disappearance of starting material and the appearance of product peaks for 2-triethylammonium salt **13**[1b] were measured. Concentrations of the product at various intervals were calculated from the intensity of the corresponding NMR signals. Data were plotted by the second-order rate law:

$$[1/(C_b-C_a)](\ln C_a/C_b)(C_b-x)/(C_a-x) = kt$$

where C_a = initial concentration of *N*-(sulfonyl)oxy) compounds and C_b = initial concentration of triethylamine. Plots of t vs log C_a/C_b $(C_b-x)/C_a-x)$ were linear for >75% of the reaction. Slopes of these plots were used to calculate second-order rate constants by:

$$k = \text{slope} \times 2.303/(C_b-C_a) \quad \text{L mol}^{-1}\,\text{s}^{-1}$$

Duplicate runs gave rate constants which were in agreement ±7.5% with the reported average values.

Deuterium Exchange Reactions of N-(Sulfonyloxy) Amides with Triethylamine in the Presence of H_2O or D_2O. Triethylamine (2.4 mmol) was added to a mixture of deuterated *N*-(sulfonyloxy) amide **4-α,α-d_2** or **6-α-*d*** (1.2 mmol) and H_2O (12 mmol) in CH_2Cl_2 (6.0 mL). The mixture was stirred for 5 min (**4-α,α-d_2**) or 24 h (**6-α-*d***) at room temperature and the reaction quenched with 1 N HCl (4.0 mL). Concentration of the organic layer gave back unreacting starting material. NMR analysis showed the same integrated ratios of protons as in the starting material, indicating that no deuterium exchange had taken place. A similar experiment with protio **5** and D_2O showed no deuterium incorporation at the α-position, indicating no exchange had occurred with **5**.

General Procedure for Synthesis of N-Alkyl-2-(alkylamino)-2-arylethanamides. To *N*-(mesyloxy) amide **4**[1b] (487 mg, 2 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added an amine (4.4 mmol) in CH_2Cl_2 (15 mL) over a period of 30 min. The resulting solution was stirred at 0 °C for 1 h and at room temperature overnight. The solvent was removed, and the residue was treated with 1 N NaOH, extracted with EtOAc (50 mL), washed with water (2 × 10 mL), and dried over $MgSO_4$. After rotary evaporation, the product was purified by flash chromatography (hexane:ethyl acetate, 6:4) or crystallization (hexane:dichloromethane).

***N*-Methyl-2-(methylamino)-2-phenylethanamide (9)** was obtained as a crude solid (310 mg, 88%) which upon flash chromatography gave a white solid (300 mg, 1.7 mmol, 85%): mp 80–81 °C (lit.[13] mp 83–84 °C); ^{1}H NMR δ 2.41 (s, 3H, NCH_3), 2.33 (s, 1H, NH, exchangeable with D_2O), 2.80 (d, J = 4.9 Hz, 3H, HCNCH_3), 4.07 (s, 1H, NCH), 7.19 (br s, 1H, NH), 7.25–7.37 (m, 5H, ArH); ^{13}C NMR δ 26.0, 35.2, 69.5, 127.3, 128.75, 139.1, 172.5; IR ($CHCl_3$) 3384, 3019, 2783, 1670, 1531, 1414, 1037 cm^{-1}.

***N*-Propyl-2-(methylamino)-2-phenylethanamide (10)** was obtained as a crude solid (300 mg, 74%) which on flash chromatography gave a solid (240 mg, 1.2 mmol, 60%): mp 56–57 °C; ^{1}H NMR δ 0.90 (t, J = 7.4 Hz, 3H, CH_3), 1.53 (sextet, J = 7.4 Hz, 2H, CH_2), 1.64 (s, 1H, NH, exchangeable with D_2O), 2.44 (s, 3H, NCH_3), 3.23 (q, J = 6.6 Hz, 2H, NCH_2), 4.04 (s, 1H, NCH), 7.31–7.38 (m, 5H, ArH), 7.17 (br s, 1H, amide NH); ^{13}C NMR δ 22.9, 35.5, 40.8, 70.0, 127.2, 128.0, 128.8, 139.6, 172.0; IR ($CHCl_3$) 3365, 3019, 2914, 1667, 1524, 1436, 1023 cm^{-1}.

The structure of **10** was confirmed by independent synthesis of both **10** and its regioisomer *N*-methyl-2-(*n*-propylamino)-2-phenylethanamide from methyl mandelate following Effenberger's method.[14] Trifluoromethanesulfonic anhydride (6.6 mmol) was stirred with (±)-methyl mandelate (6.0 mmol) in CH_2Cl_2 (60 mL) at −78 °C. Treatment with 2,6-lutidine (6.9 mmol) and addition of either propylamine (12.0 mmol) or methylamine gave a 2-amino ester. Refluxing the 2-amino ester with methylamine (40% aqueous solution, 12 molar equiv) or propylamine (12.0 molar equiv), respectively, gave the amino amides.[15] Products were purified by preparative TLC (chloroform:methanol, 95:5).

***N*-Propyl-2-(methylamino)-2-phenylethanamide (10)**, mp 56–57 °C, was found identical by mp, mixed mp, ^{1}H NMR, IR, and ^{13}C NMR to the product obtained from reaction of *N*-mesyloxy amide **4** with *n*-propylamine. The 2-methylamino group appeared as a singlet at δ 2.44.

Regioisomer of **10**, ***N*-methyl-2-(propylamino)-2-phenylethanamide**: ^{1}H NMR δ 0.93 (t, J = 7.3 Hz, 3H, CH_3), 1.52 (sextet, J = 7.3 Hz, 2H, CH_2), 1.71 (s, 1H, NH, exchangeable with D_2O), 2.83 (d, J = 5.0 Hz, 3H, NCH_3), 2.52, 2.62 (AB q, J = 5.2 Hz, 2H, CH_2), 4.15 (s, 1H, NCH), 7.30–7.39 (m, 5H, ArH), 7.26 (br s, 1H, amide NH); ^{13}C NMR δ 11.7, 23.2, 25.9, 50.7, 67.8, 127.2, 127.9, 128.7, 139.8, 173.0; IR ($CHCl_3$) 3363, 3008, 2876, 1668, 1530, 1456, 1116, 1030 cm^{-1}. The *N*-methyl amide group appeared as a doublet at 2.83 δ (J = 5.0 Hz).

***N*-*tert*-Butyl-2-(methylamino)-2-phenylethanamide (11) and *N*-methyl-2-*tert*-(butylamino)-2-phenylethanamide (12)** were obtained as a crude mixture from reaction of **4** with *tert*-butylamine (410 mg, 94%, **11**:**12** = 80:20) and separated by preparative TLC ($CHCl_3$:CH_3OH, 95:5). Compound **11** was an oil: ^{1}H NMR δ 1.34 (s, 9H, C(CH_3)$_3$), 1.67 (s, 1H, NH, exchangeable with D_2O), 2.42 (s, 3H, NCH_3), 3.90 (s, 1H, NCH), 7.03 (br s, 1H, amide NH), 7.28–7.36 (m, 5H, ArH); ^{13}C NMR δ 28.7, 35.4, 50.5, 70.4, 127.1, 127.8, 128.7, 139.8, 171.0; IR ($CHCl_3$) 3366, 3026, 2388, 1668, 1519, 1466, 1028 cm^{-1}. The three-proton singlet at δ 2.42 confirms its assignment as 2-methylamino regioisomer **11**.

Compound **12** was an oil: ^{1}H NMR δ 1.12 (s, 9H, C(CH_3)$_3$), 1.58 (s, 1H, NH, exchangeable with D_2O), 2.88 (d, J = 5.1 Hz, 3H, NCH_3), 4.31 (s, 1H, NCH), 7.86 (br s, 1H, amide NH), 7.29 (s, 5H, ArH); ^{13}C NMR δ 25.8, 29.3, 51.9, 61.8, 127.2, 127.7, 128.9, 141.7, 174.6; IR ($CHCl_3$) 3354, 2968, 2401, 1666, 1531, 1454, 1101, 1024 cm^{-1}. Samples of minor isomer **12** were always contaminated with major regioisomer **11**. However, the three-proton doublet at δ 2.88 (J = 5.08 Hz) confirmed its assignment as *N*-methyl amide regioisomer **12**.

Acknowledgment. This work was made possible by support from the National Institutes of Health (GM44529-01), which we would like to thank.

Supplementary Material Available: Copies of ^{13}C NMR spectra of new compounds **4–7** and **9–12** (14 pages). See any current masthead page for ordering information.

(13) Davtyan, S. M.; Papayan, G. L.; Asratyan, S. N. *Arm. Khim. Zh.* **1970**, *23*(4), 251–7; *Chem. Abstr* **1979**, *73*, 25030e.
(14) (a) Effenberger, F.; Burkard, U.; Willfahrt, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 65. (b) Feenstra, R. W.; Stokkingreef, E. H. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1987**, *28*, 1215.
(15) Aoyama, T.; Nakano, T.; Marumo, K.; Uno, Y.; Shiori, T. *Synthesis* **1991**, 1163.