1 H); IR (KBr) 3600–3200, 1735, 1650, 1640, 1470, 1450, 1250, 1155, 1135 cm^{-1}.

Amine 36. A mixture of **35** (30 mg, 0.03 mmol), activated Zn (65 mg), MeOH (1.5 mL), and glacial acetic acid (0.2 mL) was stirred vigorously and heated at 60 °C for 30 min. The reaction mixture was cooled, and the solids were filtered through Celite and washed with MeOH. The combined filtrates were made basic by the addition of 30% aqueous NH_4OH (5 mL) and extracted three times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), the solvents were evaporated under vacuum, and the residue was purified by flash chromatography (EtOAc) to give **36** (14 mg, 68%): ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 7, 3 H), 1.72 (q, J = 7, 2 H), 2.90 (s) and 2.95 (s) (total 6 H), 3.71 (s, 3 H), 2.8–4.6 (m, 6 H), 5.9 (m, 2 H), 6.9–7.7 (m, 4 H), 9.2 (m, 1 H); EIMS, m/e 411 (M^+), 366, 215, 170, 144.

Acknowledgment. This research was supported by PHS Grant GM 25816 awarded by the National Institute of General Medical Sciences, DHHS. GC/MS data was obtained on a VG 7070 GC/MS instrument and associated VG 2035F/B data system, funded by NIH Biomedical Research Development Grant 1 508 RR 09082.

Registry No. (±)-**4**, 33190-27-1; (±)-**5a**, 99619-21-3; (±)-**5b**, 99619-25-7; (±)-**5c**, 99619-26-8; **8**, 63-75-2; **8**·HBr, 300-08-3; (±)-**9**, 99619-13-3; (±)-**10**, 99619-14-4; (±)-**11**, 99619-15-5; **12**, 22980-09-2; (±)-**13**, 99619-16-6; (±)-**14a**, 99619-17-7; (±)-**14b**, 99619-22-4; **15a**, 99619-18-8; **15b**, 99619-23-5; (±)-**16a**, 99619-19-9; (±)-**16b**, 99619-24-6; (±)-**17a**, 99619-20-2; (±)-**17b**, 99631-60-4; (±)-**18**, 99619-27-9; (±)-**19**, 99619-28-0; **20**, 99619-34-8; (±)-**21** (isomer 1), 99619-35-9; (±)-**21** (isomer 2), 99619-48-4; (±)-**22**, 99619-29-1; **23**, 67593-15-1; **24**, 99619-30-4; **25**, 99619-31-5; **26**, 99619-32-6; **27**, 99619-33-7; (±)-**28** (isomer 1), 99619-36-0; (±)-**28** (isomer 2), 99619-45-1; (±)-**29** (isomer 1), 99619-37-1; (±)-**29** (isomer 2), 99619-46-2; (±)-**30** (isomer 1), 99619-38-2; (±)-**30** (isomer 2), 99619-47-3; (±)-**31**, 99619-39-3; **34**, 99619-40-6; (±)-**35** (isomer 1), 99619-44-0; (±)-**35** (isomer 2), 99619-49-5; (±)-**36** (isomer 1), 99631-61-5; (±)-**36** (isomer 2), 99619-50-8; **38**, 99619-41-7; (±)-**39**, 99619-42-8; **40**, 99619-43-9; $Me_3C(OMe)_3$, 1445-45-0; propylene oxide, 16033-71-9.

The Reactions of α-Arylsulfonoxy Ketones with Nucleophiles

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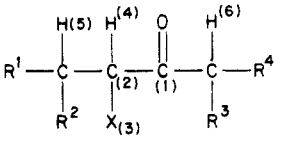
α-(*p*-Nitrophenyl)sulfonoxy ketones can be converted to α-hydroxy ketals and α-hydroxy ketones by reaction with potassium carbonate and basic or acidic workup, respectively. They also react with amines to give α-amino ketones in high yields. Nonnucleophilic amines give an intramolecular aromatic substitution in the derived enolate. Factors which dictate the reaction patterns in these compounds are discussed.

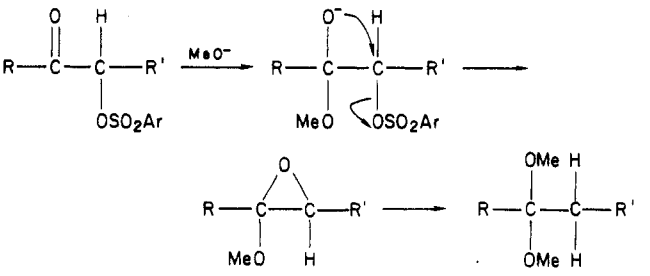
The chemistry of α-halo ketones is an area of great interest due to the wide variety of transformations they undergo. They react with both nucleophiles and bases; however, there is a variety of positions (six altogether) that may be attacked. A superb recent review details these



processes, all of which have been identified. The pathway(s) actually followed depend(s) on the structure of the substrate, the presence of α- and α′-hydrogens, the particular halogen present (chlorine or bromine), and the nucleophile/base used.[1]

α-Sulfonoxy ketones have received much less attention. Since they contain the same general features as α-halo ketones in that they have a leaving group attached next to the carbonyl group, it is not surprising that behavior similar to that of α-halo ketones has been observed for these compounds. Thus Conia has reported that they are Favorski rearrangement substrates,[2] and it is claimed that

Scheme I



α-mesyl ketones are thiol-specific electrophiles.[3]

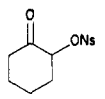
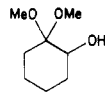
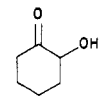
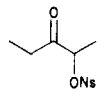
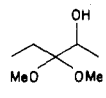
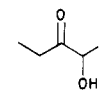
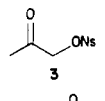
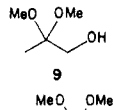
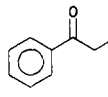
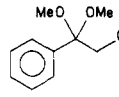
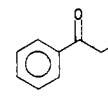
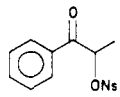
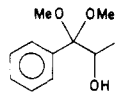
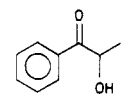
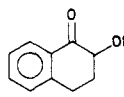
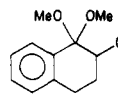
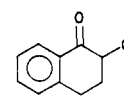
On the other hand, sulfonoxy groups are much better leaving groups than halogens. Creary has effectively exploited this property of α-sulfonoxy ketones to generate and study α-keto carbocations.[4] Furthermore, the sulfonoxy group is a strong electron-withdrawing group[5] which can acidify the α-hydrogen significantly. Some interesting chemistry of the derived anion has also been reported.[4]

We have recently described facile routes to α-arylsulfonoxy ketones by the reaction of enol esters, silyl enol

(1) Verhe, R.; De Kimpe, N. "The Chemistry of Functional Groups, Supplement D"; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons: London, 1983; p 813.
(2) Conia, J. M.; Salaun, J. R. *Acc. Chem. Res.* **1972**, *5*, 33.
(3) Simons, S. S., Jr.; Pons, M.; Johnson, D. F. *J. Org. Chem.* **1980**, *45*, 3084 and references therein.
(4) Creary, X. *Acc. Chem. Res.* **1985**, *18*, 3. This is an excellent summary of the solvolytic work done on these compounds.
(5) Lambert, J. B.; Mark, H. W.; Holcomb, A. G.; Magyar, E. S. *Acc. Chem. Res.* **1979**, *12*, 317.

0022-3263/86/1951-0130$01.50/0

Table I. Conversion of α-Nosyl Ketones to α-Hydroxy Ketals and α-Hydroxy Ketones

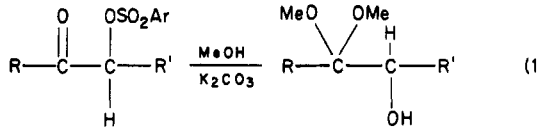
α-nosyl ketone	α-hydroxy ketal	yield,[a] %	α-hydroxy ketone	yield,[b] %
 1	 7	95	 13	75
 2	 8	71	 14	53
 3	 9	70		
 4	 10	88	 15	100
 5	 11	84	 16	100
 6	 12	100	 17	100

[a] Product isolated after basic workup. [b] Product isolated after acidic workup.

ethers, and enamines with arylsulfonyl peroxides.[6] We have undertaken a study of ketones with an α-(*p*-nitrophenyl)sulfonoxy (ONs, nosylate) substituent to determine if the arylsulfonoxy group confers exceptional reactivity to them. Our results suggest that α-arylsulfonoxy ketones, exhibit chemistry that is greatly simplified over that found for analogous α-halo ketones. We find that the carbonyl group is highly prone to nucleophilic addition and that the α proton is easily removed with sterically hindered bases.

Results and Discussion

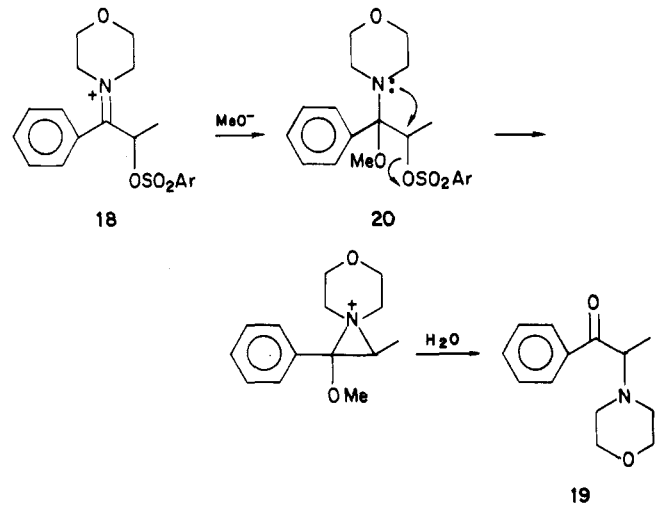
Treatment of α-(*p*-nitrophenyl)sulfonoxy ketones **1–6** with methanolic potassium carbonate followed by basic workup leads to the isolation of a single product shown to be the corresponding α-hydroxy dimethyl acetal (eq 1).



(1)

Product structures **7–12** and yields are found in Table I. These products most likely result from an intermediate epoxide which in turn stems from initial attack by methoxide on the carbonyl carbon (Scheme I). Analogous chemistry is well-known for α-halo ketones.[1] Noteworthy, however, is the fact that only a single product is produced. Careful examination of the reaction mixture gave no evidence for α-methoxy ketone, the product of direct nucleophilic displacement of the nosyl group. Similar behavior has been reported for several α-keto mesylates[7] and

Scheme II

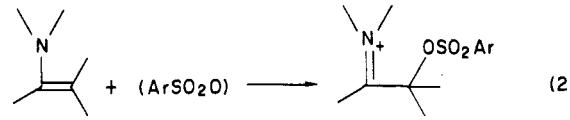


triflates,[8] and the present results indicate that carbonyl addition by alkoxides is the sole process of α-sulfonoxy ketones. On the other hand, α-halo ketones usually give mixtures of products that depend heavily on structure and conditions.[1,9]

Apparently the inductive effect of the sulfonoxy group strongly activates the carbonyl group toward attack by the methoxide, so much so that other pathways do not compete effectively. Direct substitution of the sulfonoxy group can be accomplished when weak nucleophiles are used such as fluoride.[10]

When the reaction mixture is treated with dilute acid, then α-hydroxy ketones are isolated in yields reported in Table I. In general, better yields are obtained by direct hydrolysis of the reaction mixture rather than by isolation of the hydroxy ketal and then hydrolysis. The same observation has been made by Moriarty.[11] Thus merely by choice of workup, α-nosyl ketones can be converted to α-hydroxy ketals or acyloins simply and in high yields.

If the high reactivity of the carbonyl group in α-nosyl ketones toward alkoxide nucleophiles proved general for other nucleophiles (specifically amines), then a great deal of interesting chemistry might evolve. Some indication of the profit in this approach was obtained in experiments with α-arylsulfonoxy iminium ions generated in situ from the reaction of enamines and arylsulfonyl peroxides (eq 2). These iminium ions are presumed to be the first

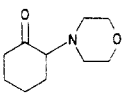
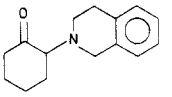
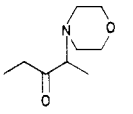
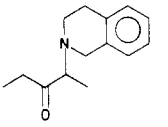
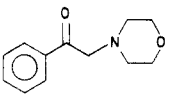
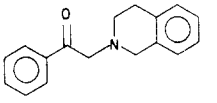
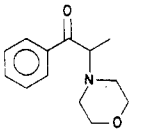
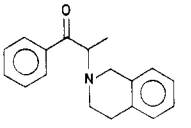


(2)

formed products in the synthesis of α-nosyl ketones from enamines.[6b] When methanol and potassium carbonate were added to a solution of **18**, four products were formed. Three of these were found to be propiophenone, α-hydroxy ketal, **11**, and α-hydroxy ketone, **16**. Propiophenone presumably results from hydrolysis of unreacted enamine, and the hydroxylated products most likely come from α-nosyl ketone, **5**, produced by hydrolysis of **18**. No attempts were

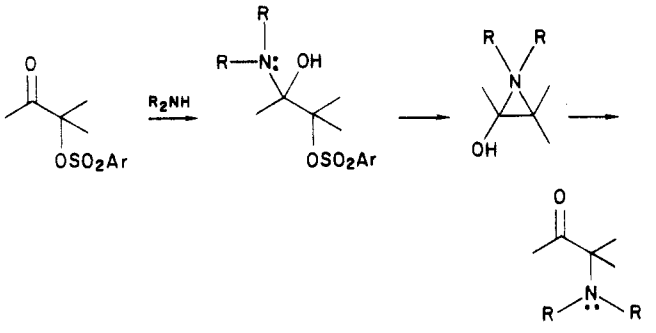
(6) (a) Hoffman, R. V. *Synthesis* **1985**, 760. (b) Hoffman, R. V.; Jankowski, B. J.; Carr, S. C. *J. Org. Chem.*, in press.
(7) Creary, X. *J. Am. Chem. Soc.* **1984**, *106*, 5568.
(8) Creary, X.; Rollin, A. J. *J. Org. Chem.* **1977**, *42*, 4226.
(9) See, for example: Turro, N. J.; Gagosian, R. B.; Rappe, C.; Knutsson, L. *J. Chem. Soc. D* **1969**, 270. Stevens, C. L.; DeYoung, J. J. *J. Am. Chem. Soc.* **1954**, *76*, 718. Liotta, C. L.; Harris, H. P. *Ibid.* **1974**, *96*, 2250.
(10) Keisewetter, D. O.; Katzenellenbogen, J. A.; Kilbourn, M. R.; Welch, M. J. *J. Org. Chem.* **1984**, *49*, 4900.
(11) Moriarty, R. M.; Hou, K. C. *Tetrahedron Lett.* **1984**, *25*, 691.

Table II. Reaction of α-Nosyl Ketones with Amines

α-nosyl ketone	morpholine product	morpholine yield,[a]	1,2,3,4-tetrahydroisoquinoline product	1,2,3,4-tetrahydroisoquinoline yield,[a] %
1	 21	94	 26	76
2	 22	64	 27	65
4	 23	85	 28	96
5	 24	81	 29	91

[a] Isolated yields of purified product.

Scheme III



made to rigorously exclude water. The fourth, and major, product was α-morpholinopropiophenone, **19**, which must result from a 1,2-migration of the amino constituent. The simplest route to this material from **18** would be addition of methoxide to yield a tetrahedral intermediate, **20**, followed by closure to an aziridine. Hydrolysis yields **19** (Scheme II). Again no direct substitution of nosylate by methoxide was detected, although this is a common product in the reaction of alkoxides with α-halo imines.[12]

Our experience with α-nosyl ketones thus suggested that amine nucleophiles might add to the carbonyl group to give a structurally analogous tetrahedral intermediate (Scheme III). Closure to either an aminooxirane or a hydroxyaziridine might occur, but the greater nucleophilicity of nitrogen would favor the latter. Hydrolytic workup would deliver the α-amino ketone product.

We were gratified to find that treatment of α-nosyl ketones **1**, **2**, **4**, and **5** with morpholine or 1,2,3,4-tetrahydroisoquinoline leads in each case to a single new product identified as the α-amino ketone in yields indicated in Table II. This method provides a simple, efficient route to α-amino ketones of diverse structure.

While this α-substitution product could arise from direct displacement of the nosylate, our experience with the α-nosyl iminium system suggests that attack at the carbonyl carbon followed by 1,2-migration of the amine nucleophile is also highly likely. In view of the apparently high propensity of α-arylsulfonyl ketones to undergo nucleophilic carbonyl addition, we prefer the latter path. Direct substitution is not, however, excluded by our results.

(12) De Kimpe, N.; Verhe, R. In "The Chemistry of Functional Groups, Supplement D"; Patai, S., Rappoport, Z., Eds., John Wiley and Sons: London, 1983; p 549.

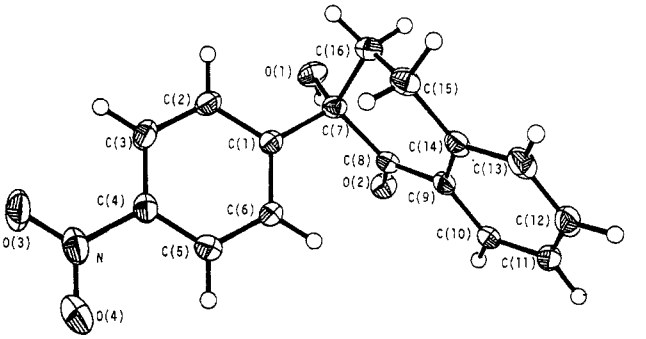
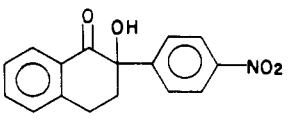
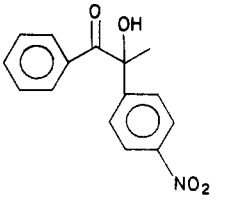


Figure 1. Structure (ketol **30**) confirmation by single-crystal X-ray diffraction.

In an attempt to investigate the base-promoted chemistry of α-nosyl ketones, nosyltetralone, **6**, was treated with the nonnucleophilic base, DBU, in benzene. Rapid decomposition (30 min) of the reactant was accompanied by the formation of a single product which proved to be ketol **30** (77%). The structure was confirmed by single-crystal X-ray diffraction (Figure 1). Similar chemistry was seen for **5** which gave ketol **31** (45%) under the same conditions.



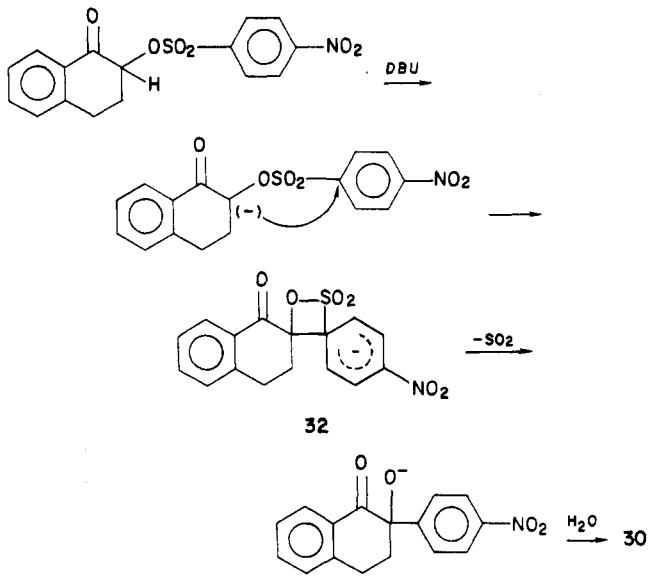
30



31

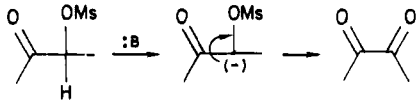
The unusual product, **30**, is formed by the loss of sulfur dioxide from **6**. The most reasonable pathway for its formation (Scheme IV) is dependent on the strong electron-withdrawing ability of the α-nosyl group which acidifies the α-proton significantly. Since the base is

Scheme IV



nonnucleophilic and does not add to the carbonyl group, α-proton removal to the enolate is followed by ipso attack on the activated *p*-nitrobenzene ring. The presumed four-membered ring intermediate, **32**, opens to give sulfur dioxide and the alkoxide. The sulfur dioxide is apparently scavenged by a second equivalent of base since 2 equiv are required for complete reaction. Furthermore, the catalytic role of the base is assured since the same products were found when DBN was employed.

The formation of α-sulfonoxy enolates has been observed by Creary for α-mesyl and α-triflyl ketones. In general these anions undergo reductive elimination to a diketone (eq 3).[4] In the present cases, the *p*-nitro group facilitates



(3)

attack on the aromatic ring, and the diketone is not observed. The analogous formation of α-halo enolates has been detected by deuterium exchange,[13] but the equilibrium is unproductive in terms of further reactions.

In summary, we find that α-sulfonoxy ketones undergo two modes of reaction with nucleophiles/bases. The favored reaction appears to be addition to the carbonyl group followed by intramolecular displacement of the sulfonoxy group in the resulting tetrahedral intermediate. The arylsulfonoxy group is probably responsible for this selectivity since its electron-withdrawing power activates the carbonyl group toward nucleophilic addition, and its excellent leaving ability ensures rapid conversion of the tetrahedral intermediate to product.

When the base is nonnucleophilic, α-enolate formation and conversion to products are found. Again the sulfonoxy group dictates the reaction course since it acidifies the α-proton significantly[14] and then provides a reaction path by which the enolate can proceed to product.

This work has utilized garden-variety α-sulfonoxy ketones and reaction conditions. There is good reason to predict that there are structural limits to the general behavior we have observed. Indeed Creary has reported that severe crowding reduces the kinetic acidity of the α-proton in α-sulfonoxy ketones, and other unusual base-promoted chemistry is observed.[16] Nevertheless, α-arylsulfonoxy ketones exhibit excellent selectivity in their reactions. They thus have great potential as intermediates for a variety of useful transformations.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer 283 spectrophotometer as potassium bromide disks for solids or as thin films for neat liquids. Proton NMR spectra were obtained on either a JEOL PS-100 or a Varian XL-200 instrument. Chemical shifts are reported for chloroform-*d* solution in ppm relative to Me_4Si. Carbon-13 NMR spectra were recorded on a Varian XL-200 spectrometer. Chemical shifts are reported in ppm downfield from Me_4Si. An APT pulse sequence was used to determine the numbers of hydrogens bound to each carbon. Mass spectra were obtained on a Hitachi RMU-6 instrument. Elemental analyses were performed by Micanal., Tuscon, AZ. Thin-layer chromatography was performed on Eastman silica gel sheets.

Nosyl ketones **1–6** were prepared according to the literature method using enol acetates.[6a]

Reaction of α-Nosyl Ketone 1 with Potassium Carbonate in Methanol. Basic Workup. A solution of **1** (235 mg, 0.79 mmol) in methanol (15 mL) was cooled to 0 °C, and powdered potassium carbonate (275 mg, 1.99 mmol, 5 equiv) was added all at once. The reaction mixture was stirred at room temperature for 15 min at which time TLC analysis (silica gel, chloroform) showed that all the starting nosylate was consumed. The reaction was filtered and evaporated by rotary evaporation. Methylene chloride (15 mL) was added to the residue, and the mixture was again filtered to remove residual salts. Evaporation of the solution gave a pale yellow oil (120 mg, 95%) that had an NMR spectrum identical with that reported for **7**.[17] No other components were detected in the NMR nor by gas chromatography. The product was further purified by Kugelrohr distillation. In addition to the NMR spectrum, the IR spectrum had a broad OH absorption at 3660 cm^{-1} and a very strong band centered at 1060 cm^{-1} for the acetal function. The mass spectrum had *m/e* 160 (M^+), 129 ($M^+ - OCH_3$), 101 (base peak, $M^+ - CH_2CH_2CH_2OH$).

The same procedure was used for **2–6**. In all cases the hydroxy ketal was the only product detected. Identification of the products was confirmed by comparison of spectral data with that available in the literature. New data for these are reported.

Hydroxy ketal 8: described completely in ref 11.

Hydroxy ketal 9:[18] IR (neat) cm^{-1} 3500 (O–H), 1100–1040 (br, acetal C–O); NMR δ 3.42 (s, 2 H, CH_2OH), 3.17 (s, 6 H, CH_3), 1.25 (s, 3 H, CH_3); mass spectrum, *m/e* 120 (M^+), 105 ($M^+ - CH_3$), 89 ($M^+ - CH_2OH$).

Hydroxy ketal 10: described completely in ref 11.

Hydroxy ketal 11:[19] IR (neat) cm^{-1} 3490 (OH), 1030–1100 (acetal C–O); NMR δ 7.35 (br s, 5 H, Ar CH), 3.97 (q, 1 H, J = 6 Hz, $CH(OH)CH_3$), 3.35 (s, 1 H, OH), 3.16 (s, 6 H, OCH_3), 0.96 (d, 3 H, J = 6 Hz, $CHCH_3$); mass spectrum, *m/e* 151 (base peak, $M^+ - CH(OH)CH_3$), 121, 105, 77.

Hydroxy ketal 12:[18] IR (neat) cm^{-1} 3470 (OH), 1030–1085 (br, acetal C–O); NMR δ 7.47 (m, 1 H, *o*-CH), 7.16 (m, 3 H, Ar CH), 4.12 (m, 1 H, $CH(OH)$), 3.20 (s, 3 H, OCH_3), 3.11 (s, 1 H, OH), 2.94 (s, 3 H, OCH_3), 2.70 (m, 2 H, benzylic CH_2), 1.99 (m, 2 H, CH_2); mass spectrum, *m/e* 177 ($M^+ - OCH_3$), 176 ($M^+ - CH_3OH$), 119, 117 (base peak, $M^+ - 91$), 91.

Reaction of α-Nosyl Ketone 1 with Potassium Carbonate in Methanol. Acidic Workup. The reaction was carried out as described. When the starting material was gone, the reaction mixture was filtered and evaporated. Methylene chloride (25 mL) was added to the residue, and the mixture was extracted with 2.5 M hydrochloric acid (2 × 15 mL). The organic layer was dried

(13) Bordwell, F. G.; Carlson, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3377.
(14) The p*K*a's of the amidine bases are about 12[15] and they effectively remove the α-proton. Thus the p*K*a at the α-position bearing the sulfonoxy group is considerably less than the normal value of about 20.
(15) Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley-Interscience: New York, 1975; p 166.
(16) Creary, X. *J. Org. Chem.* **1980**, *45*, 2419.
(17) Creary, X.; Rollin, A. J. *J. Org. Chem.* **1977**, *42*, 4231.
(18) Stevens, C. L.; Beereboom, J. J.; Rutherford, K. G. *J. Am. Chem. Soc.* **1955**, *77*, 4590.
(19) Stevens, C. L.; Malik, W.; Pratt, R. *J. Am. Chem. Soc.* **1950**, *72*, 4758.

($MgSO_4$) and evaporated to give a pale oil that slowly solidifies (75%). The hydroxy ketone **13** was identified by comparison of its IR[20] and mass spectral data[21] with literature data. No other products were detected by TLC (silica gel:chloroform) or in the NMR spectrum.

Nosylates **2**, **4–6** were reacted and worked up similarly to give the corresponding hydroxy ketone in yields listed in Table I. The hydroxy ketones **14**,[22] **15**,[23] **16**,[24] and **17**[25] were identified by comparison of spectral data with literature values. In all cases only a single product was obtained and was of quite good purity. Attempts to further purify the products by Kugelrohr distillation or column chromatography were often thwarted by dimerization of the hydroxy ketone.

Reaction of α-Nosyl Ketone 1 with Morpholine. Morpholine (175 mg, 2 mmol) was added to a solution of **1** (300 mg, 1 mmol) in methylene chloride (35 mL), and the mixture was stirred at room temperature for 64 h until TLC analysis (silica gel:chloroform) indicated that the starting material was gone. The reaction was filtered to remove the morpholine salt and extracted with 2.5 M HCl. The acidic extracts were made basic (6 M NaOH) and extracted with methylene chloride, and the organic layer was dried and evaporated to give a light yellow oil (170 mg, 94%) that was a single compound by TLC and spectral analysis. Further purification was accomplished by Kugelrohr distillation. The material was identified as 2-morpholinocyclohexanone, **21**: IR cm^{-1} 1712 (C=O), 1116 (C–O); ^1H NMR δ 3.7 (m, 4 H, OCH_2), 2.90 (d of d, 1 H, J = 12, 7 Hz, α-CH), 2.55 and 1.92 (m's, 12 H total, ring CH_2); mass spectrum, m/e 183 (M^+), 155 ($M^+ - CO$), 126 (base peak), 112, 97, 69; exact mass calcd for $C_{10}H_{17}NO_2$ 183.1260, found 183.1244. The material could not be converted to a stable product for elemental analysis as attempted salt formation or alkylation gave cleavage products.

Nosyl ketones **2**, **4**, and **5** were reacted with morpholine and worked up similarly to give the α-morpholino ketones **22–24** in yields reported in Table II. As before only a single product was detected. Structure identification was accomplished from spectral data.

2-Morpholino-3-pentanone (22): IR cm^{-1} 1710 (C=O), 1450 (CH_3), 1115 (OCH_2); ^1H NMR δ 3.70 (m, 4 H, OCH_2), 3.11 (q, 1 H, J = 6 Hz, C(O)CH), 2.58 and 2.50 (q overlapping m, 6 H total, J = 7 Hz, CH_3CH_2 and NCH_2), 1.14 (d, 3 H, J = 6 Hz, $CHCH_3$), 1.04 (t, 3 H, J = 7 Hz, CH_2CH_3); mass spectrum, m/e 171 (M^+), 156 ($M^+ - CH_3$), 114 ($M^+ - CH_3CH_2C{=}O\cdot$), 86 (M^+ – morpholino·), 83, 70.

2-Morpholinoacetophenone (23): IR cm^{-1} 1680 (C=O), 1600 (C=C); ^1H NMR δ 7.95 (d, 2 H, ortho H's), 3.47 (m, 3 H, Ar H's), 3.80 (s, 2 H, CH_2), 3.75 (m, 4 H, OCH_2); mass spectrum, m/e 105 (M^+), 105 ($C_6H_5C{=}O^+$), 100 ($M^+ - C_6H_5C{=}O\cdot$), 77 ($C_6H_5^+$); exact mass calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1091.

2-Morpholinopropiophenone (24): IR cm^{-1} 1682 (C=O), 1600 (C=C), 1450 (CH_3), 1115 (OCH_2); ^1H NMR δ 8.09 (m, 2 H, ortho H's), 7.48 (m, 3 H, Ar H's), 4.04 (q, 1 H, J = 7 Hz, methine H), 3.68 (m, 4 H, OCH_2), 2.62 (m, 4 H, NCH_2), 1.24 (d, 3 H, J = 7 Hz, CH_3); mass spectrum, m/e 219 (M^+), 204 ($M^+ - CH_3$), 151 ($M^+ - 68$), 133 (M^+ – morpholine), 114 (base peak, $M^+ - C_6H_5C{=}O\cdot$), 105, 77. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.01; H, 7.83; N, 6.37.

Reaction of α-Nosyl Ketone 1 with 1,2,3,4-Tetrahydroisoquinoline. 1,2,3,4-Tetrahydroisoquinoline (266 mg, 2 mmol) was added to a solution of **1** (299 mg, 1 mmol) in methylene chloride (35 mL), and the mixture was stirred for 72 h at room temperature. The reaction was filtered to remove the ammonium salt formed and extracted with 2.5 M HCl. The aqueous layer was made basic (6 M NaOH) and extracted with methylene chloride, and the organic layer was dried ($MgSO_2$) and evaporated to yield a pale oil (200 mg) that was found to be predominantly the α-amino ketone **26** (76%) and some unreacted tetrahydroisoquinoline. These were difficult to separate since the amino ketone tended to decompose upon chromatography. A fairly pure sample was obtained by Kugelrohr distillation, but small amounts of starting amine were present in the product. However, the yield of amino ketone corresponded closely to the amount of ammonium salt produced in the reaction: IR cm^{-1} 1710 (C=O); NMR δ 7.04 (m, 4 H, Ar H's), 3.99 (s, 2 H, $C_6H_4CH_2N$), 3.77 (dd, 1 H, J = 9 Hz, J = 1.7 Hz, CHN), 3.15 (m, 2 H, NCH_2), 2.85 (m, 4 H, $ArCH_2CH_2$ and $C(=O)CH_2$), 2.1–1.4 (m, 6 H, ring H's); mass spectrum, m/e 229 (M^+), 201 ($M^+ - CO$), 132 ($M^+ - C_6H_9O$), 104 (o-xylylene); exact mass calcd for $C_{15}H_{19}NO$ 229.1467, found 229.1390.

Nosyl ketones **2**, **4**, and **5** were reacted with 1,2,3,4-tetrahydroisoquinoline analogously to deliver the α-*N*-tetrahydroisoquinolinyl ketones **27–29**. Due to the difficulties in removing all of the amine, the product always contained small amounts of this reactant. It was evident that only one component was produced in the reaction. A variety of separation methods based on either

Table III. Summary of Crystal and Data Collection Parameters for 30

FW = 283.3
$F(000)$ = 592
space group $P2_1/c$ (no. 14)
formula units/unit cell = 4
density (measurd) = na
density (cald) = 1.42 g cm^{-3}
μ(Mo Kα) = 0.96 cm^{-1}
data crystal size = 0.207 × 0.276 × 0.460 mm
cell parameters[a]
  a = 13.7402 (21) Å
  b = 10.8517 (17) Å
  c = 8.8756 (13) Å
  β = 91.351 (12)°
  vol = 1323.0 (3) $Å^3$
θ–2θ data collection parameters[b]
  data collectn temp 20 (2) °C
  scan range: 1.25° below 2θ ($K\alpha_1$), 1.25° above $2\theta(K\alpha_2)$
  scan speed: 6–30 deg min^{-1}
  tot. background counting time/tot. scan time = 0.5
  2θ limits: 1 $\langle \pm h,k,l \rangle$ 60°
3 standards collected every 141 reflectns
  500, 230, 004
absorption correction based on azimuthal scans
  R before correction = 3.13%. R after correction = 2.69%
  maximum and minimum transmission: 0.901/0.811
4434 reflections collected
3901 unique, space-group allowed reflections
1659 reflections observed, with $F > 5\ \sigma$ (F)
structure solution[c]
  agreement with all non-hydrogen isotropic, $R(F)$ = 16.55%
  agreement with all non-hydrogen anisotropic, $R(E)$ = 8.81%
final agreement factors
  $R(F) = \sum||F_o| - |F_c||/\sum|F_o|$ = 5.39%
  $wR(F) = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ = 5.13%
  $S = GOOF = [\sum w(|F_o| - |F_c|)^2/(m - n)]^{1/2}$
  m = number of reflections (1659)
  n = number of parameters (193) = 1.501
  $w = 1/[\sigma^2(F) + |g|F^2]$, g = 0.00043.
for final cycles the least-squares shift to error
  max. = –0.025 for U(23) of C(16)
  av. = 0.003
structure factor calculations including all reflections
  $R(F)$ = 12.84%, $wR(F)$ = 8.38%
final difference map:
  max. peak height: 0.189 $eÅ^{-3}$
  min. peak trough: –0.236 $eÅ^{-3}$

[a] Obtained by least-squares fit to the setting for 25 reflections. Reflections are in the range $13 < 2\theta < 40°$. [b] For the Nicolet P3/F diffractometer equipped with a graphite monochromator. [c] By direct methods with use of Shelxtl Rev. 3, Nicolet XRD, Madison, WI. Structure refinement (Shelxtl Rev. 3 (1981), Nicolet XRD, Madison WI). Blocked cascade least-squares refinement refines on F and uses anomalous dispersion factors for atoms with atomic numbers >2. Neutral atom atomic scattering factors (taken from International Tables Vol. IV) are used unless otherwise noted.

(20) Sheehan, J. C.; O'Neill, R. C.; White, M. A. *J. Am. Chem. Soc.* **1950**, *72*, 3376.
(21) Strobel, M. P.; Morin, L.; Paquer, D. *Tetrahedron Lett.* **1980**, *21*, 523.
(22) Pechal, M.; Cvengrosova, Z.; Holotik, S.; Malik, L.; Hrusorsky, M. *J. Chromatogr.* **1981**, *206*, 541.
(23) Sadtler standard spectra: ^1H NMR 17161 M, IR (grating) 24179K.
(24) Bolus, S. B.; Katzenellenbogen, J. A. *J. Org. Chem.* **1974**, *39*, 3309.
(25) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

volatility or chromatographic behavior were tried to circumvent this problem, but all were unsuccessful, primarily because the amino ketone degraded. For this reason elemental analysis was not productive. Furthermore, unlike the morpholine derivatives, the tetrahydroisoquinoline products did not give parent ions in the mass spectrum so exact mass determination could not be accomplished. Spectral data were used to establish the structures. Yields were calculated from integrals in the NMR spectrum and matched well the yield of salt produced.

2-(*N*-Tetrahydroisoquinolyl)-3-pentanone (27): IR cm^{-1} 1710 (C=O); ^1H NMR δ 7.05 (br s, 4 H, Ar H's), 3.96 (s, 2 H, Ar CH_2N), 3.31 (q, J = 7 Hz, 1 H, C(=O)CH), 3.2–2.5 (m, 6 H, ring H's and C(=O)CH_2), 1.20 (d, 3 H, J = 7 Hz, CHCH_3), 1.04 (t, 3 H, J = 7 Hz, CH_2CH_3);mass spectrum, m/e 160 (M^+ - CH_3CH_2C=O·), 132 (isoquinolinium), 104 (*o*-xylylene).

2-(*N*-Tetrahydroisoquinolyl)acetophenone: IR cm^{-1} 1685 (C=O); NMR δ 7.80 (d, 2 H, ortho H's), 7.4–7.0 (m, 7 H, Ar H's), 5.24 (s, 2 H, C(=O)CH_2), 4.07 (s, 2 H, Ar CH_2N), 3.20 (br t, 2 H, NCH_2), 2.85 (br t, 2 H, Ar CH_2); mass spectrum, m/e 147 (M^+ - *o*-xylylene), 146 (M^+ - C_6H_5C=O·), 132 (isoquinolinium), 119 ($C_6H_5C(O)CH_2^+$), 105, 104.

2-(*N*-Tetrahydroisoquinolyl)propiophenone (29): IR cm^{-1} 1681 (C=O); NMR δ 8.12 (m, 2 H, ortho H's), 7.43 (m, 3 H, Ar H's), 7.05 (m, 4 H, Ar H's), 4.25 (q, 1 H, J = 6 Hz, C(=O)CH), 3.82 (s, 2 H, Ar CH_2N), 3.10 (m, 2 H, NCH_2), 2.80 (m, 2 H, Ar CH_2CH_2), 1.36 (d, 3 H, J = 6 Hz , CH_3); mass spectrum, m/e 160 (M^+ - C_6H_5C=O·), 133 (M^+ - isoquinolyl), 132 (isoquinolyl), 105, 104.

Reaction of 6 with DBU. Nosylate **6** (347 mg, 1 mmol) was added as a solid to an ice-cooled, stirred solution of DBU (300 mg, 2 mmol) in benzene (15 mL). After the addition, the mixture was removed from the ice bath and stirred at room temperature. Monitoring by TLC (chloroform/hexane, 3:1) showed that the starting material was gone after 30 min, and a single new component was formed. The dark brown reaction mixture was quenched in 2.5 M HCl (15 mL) whereupon the color faded to a very pale yellow. The layers were separated, and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were extracted with saturated brine, dried ($MgSO_4$), and evaporated to give a pale yellow oil (220 mg, 78%). The crude product was a single compound which could be crystallized from carbon tetrachloride to give a pale yellow solid, mp 123–124 °C, that was analytically pure. The structure of ketol **30** was inferred from the spectral data obtained for the compound: IR cm^{-1} 3500 (OH), 1685 (C=O), 1600 (Ar C=C), 1505 (NO_2); ^1H NMR δ 8.18 and 7.51 (AA'XX' quartet, 4 H, *p*-$C_4H_4NO_2$ group), 8.23 (d, 1 H, H-ortho to C=O), 7.7–7.3 (m, 3 H, Ar H's), 4.38 (s, 1 H, OH, exchangeable with D_2O), 3.1–2.5 (AA'BB' multiplet, 4 H, CH_2CH_2); ^{13}C NMR δ 190.5 (C=O), 142.1, 141.1, 137.8, and 125.5 (quaternary Ar C's), 129.0, 123.6, 122.4, 121.9, 121.6, and 118.3 (tertiary Ar C's), 73.5 (COH), 35.2 and 25.0 (ring CH_3); mass spectrum, m/e (relative intensity) (M^+, 46), 265 (M^3 - 18, 6), 151 (41), 150 ($NO_2C_6H_4CO^+$, 100), 134 (16), 133 (19), 118 ($OCC_6H_4CH_2$, 83), 90 (51). Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.59; N, 4.95. Found: C, 66.93; H, 4.54; N, 4.74.

The same material was produced in identical yield if DBN were used as the base. If only 1 equiv of base was added, the reaction proceeded smoothly and then stopped before all of **6** was consumed. Addition of a second equivalent of base lead to rapid completion of the reaction.

Reaction of 5 with DBU. Nosylate **5** (335 mg, 1 mmol) was added as a solid to an ice-cooled, stirred solution of DBU (304 mg, 2 mmol) in benzene (15 mL). After the addition, the mixture was removed from the ice bath and stirred at room temperature. Monitoring by TLC (chloroform/hexane, 3:1) showed that the starting material was gone after 1.5 h. The yellow reaction mixture was quenched in 2.5 M HCl (15 mL) and the color faded; the layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were extracted with saturated brine (10 mL), dried ($MgSO_4$), and evaporated to yield a pale yellow oil (115 mg, 45%) that was identified as the hydroxy ketone **31**. An analytical sample was recrystallized from carbon tetrachloride/hexane: IR cm^{-1} 3450 (OH), 1665 (C=O), 1601 (C=C), 1510 (NO_2); ^1H NMR δ 8.28 and 7.70 ($\alpha\alpha'$XX' quartet, 4 H total, J = 2.3 Hz, $C_6H_4NO_2$ group), 7.75 (d, 2 H, ortho H's), 7.60–7.30 (m, 3 H, Ar H's), 4.64 (s, 1 H, OH, exchangeable with D_2O), 1.96 (s, 3 H, CH_3); ^{13}C NMR δ 196.0 (C=O), 146.4, 144.3, and 129.8 (quaternary Ar C's), 130.6, 127.3, 125.7, 124.1, and 121.4 (Ar C's), 77.3 (COH), 26.2 (CH_3). Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.79; N, 5.16. Found: C, 66.04; H, 4.82; N, 5.16.

X-ray Structure Determination of 30. A summary of the crystal and data collection parameters for **30** is given in Table III.

Acknowledgment. This work was supported in part by the National Science Foundation to whom we are indebted. We also thank Professor Edwin Vedejs, University of Wisconsin, for making available spectral data of **17**. Tetrahydroisoquinoline was a gift of Kawaken Chemicals, Ltd. We especially thank Mr. C. R. Weisenberger of The Ohio State University for making the exact mass determinations.

Registry No. **1**, 98990-62-6; **2**, 98990-63-7; **3**, 98990-66-0; **4**, 55660-72-5; **5**, 98990-64-8; **6**, 98990-65-9; **7**, 63703-34-4; **8**, 90054-91-4; **9**, 99547-44-1; **10**, 28203-05-6; **11**, 73611-99-1; **12**, 83022-55-3; **13**, 533-60-8; **14**, 5704-20-1; **15**, 582-24-1; **16**, 5650-40-8; **17**, 64559-97-3; **18**, 99547-45-2; **19**, 71867-90-8; **21**, 14909-84-3; **22**, 66388-61-2; **23**, 779-53-3; **24**, 5650-45-3; **26**, 99547-46-3; **27**, 99547-47-4; **28**, 5653-11-2; **29**, 99547-48-5; **30**, 99547-49-6; **31**, 99547-50-9; propiophenone, 93-55-0; morpholine, 110-91-8; 1,2,3,4-tetrahydroisoquinoline, 91-21-4.

Supplementary Material Available: Atomic positional parameters, atomic thermal parameters, and bond distances and angles (Tables IV–IX) (2 pages). Ordering information is given on any current masthead page.