In view of the assignment of 2 to stereochemistry **2a** and the observation that the bridge protons (5) absorb at δ 1.53, there being no high-field resonance, we conclude that steric deshielding of the 5s protons in compounds such as **1** is operative.

Experimental Section

Proton magnetic resonance spectra were obtained in $CDCl_3$ on a Bruker 90-MHz spectrometer and are reported downfield from an internal tetramethylsilane (TMS) standard. Diels–Alder adducts were prepared according to literature procedures.[4] We did find that the Diels–Alder reaction could be efficiently carried out in an annealed glass pressure bottle (Fisher and Porter) fitted with a pressure gauge, gas inlet, and pressure-release valve. Standard chromatographic and liquid–liquid extraction procedures were applied where appropriate.

Acknowledgment. Financial support from Wesleyan University and a fellowship to one of us (J. M.) are gratefully acknowledged. We especially wish to thank Dr. T. H. Regan of the Eastman Kodak Co. for obtaining the 90-MHz spectra for us.

Registry No.—**1**, 15914-94-0; **2a**, 50415-43-5.

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Nucleophilic Reactions of α-Bromoacetophenone Oxime. Preparation of *anti*-Acetophenone Oxime

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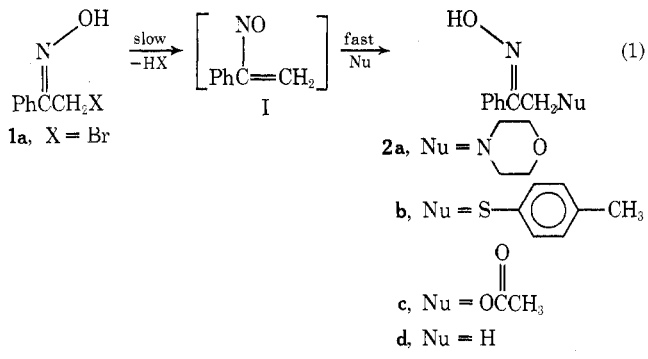
We have recently described the reaction of α-halo oximes with nucleophiles which involves the stereoselective trapping of a reactive intermediate.[1] This reaction can be summarized by eq 1, where X is halogen and Nu is a nucleophile. As shown, it was suggested that the intermediate might be α-nitrosostyrene (I), which reacts more rapidly in the s-trans conformation than in the s-cis, giving the thermally unstable anti alkyl aryl ketoxime isomer.[2] The preparation of the previously unknown *anti*-α-bromoacetophenone oxime from **2a** which had been obtained by the route of eq 1 was also reported.[1b] To explore the general synthetic utility of this reaction and to gain further insight into its mechanism, we have varied the nature of the nucleophile Nu in eq 1. In the present communication we report the results of this investigation, including the facile, one-step conversion of **1a** to *anti*-acetophenone oxime (**2d**), a previously unisolated material.



(1)

When **1a** dissolved in acetonitrile is added to an aqueous acetonitrile solution of $NaBH_4$, rapid evolution of a gas takes place. After 5 min at room temperature, extraction of the reaction mixture gives in high yield *anti*-acetophenone oxime (**2d**). In the nmr spectrum ($CDCl_3$), absorption due to the methyl group of **2d** occurs at δ 2.20 ppm while the corresponding resonance in the syn isomer is detected at 2.28 ppm.[3] The uv spectrum for **2d** in ethanol has λ_{max} 235 nm (log ϵ 3.86) compared to λ_{max} 245 nm (log ϵ 4.10) for the syn isomer. This difference is in agreement with previously reported spectra for isomeric alkyl aryl oximes.[1a,4] When **2d** was refluxed in chlorobenzene solution, there was a gradual decrease in intensity of the methyl resonance at 2.20 ppm and a corresponding increase in intensity of a peak at 2.28 ppm, resulting in a final mixture composed of 5% **2d** and 95% of the thermally generated product. This material was isolated and identified as *syn*-acetophenone oxime. A sample of **2d** was subjected to Beckmann rearrangement conditions and the major product obtained was *N*-methylbenzamide, confirming the stereochemical assignment.[5]

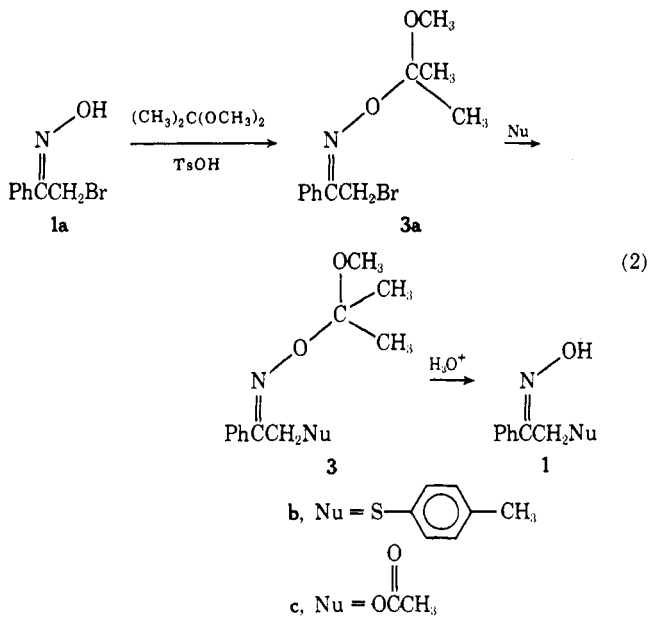
The borohydride reduction of **1a** to give **2d** takes place in ethanol and 1,2-dimethoxyethane as well as in aqueous acetonitrile. In each of these solvents, 1 mol of $NaBH_4$ is required for each mole of **1a** reduced. When 0.5 mol of $NaBH_4$ is used, 50% of **1a** is converted to **2d** while the remaining 50% is recovered. The reaction was complete within 5 min at room temperature and longer reaction times did not affect the yields or isomeric composition of the product. In a control experiment, *syn*-acetophenone oxime was recovered unreacted from an aqueous acetonitrile solution of $NaBH_4$. This finding agrees with results of previous workers.[6]

The conversion of **1a** to **2d** is thought to proceed *via* intermediate I of eq 1. The HBr produced would be expected to react with $NaBH_4$ to release hydrogen gas. If intermediate I is in fact α-nitrosostyrene, as has been proposed,[1b] then the postulated $NaBH_4$ reduction of I would be reasonable. It is known that the carbon–carbon double bond of 1-nitro alkenes[7] and α,β-unsaturated aldehydes and ketones[8] can be reduced by $NaBH_4$ to give the corresponding 1-nitro alkanes and saturated alcohols. Conjugate addition of borohydride to the proposed α-nitrosostyrene would result in an oxime product which is inert to further reduction. The anti stereochemistry of the product is in agreement with the previous results obtained with displacement by morpholine.[1]

We have also investigated the reaction of **1a** with sulfur and oxygen nucleophiles. When *p*-tolyl thiolate is added to **1a** in aqueous solution, the product isolated is *anti*-α-(*p*-tolylthio)acetophenone oxime (**2b**). The nmr spectrum ($CDCl_3$) of **2b** is similar to that of the syn isomer **1b**, prepared by an independent route (eq 2), except that the methylene resonance is shifted upfield by 0.27 ppm (δ 4.17 for the syn isomer and δ 3.90 for the anti isomer).[3] Thermal isomerization of **2b** in $CDCl_3$ resulted in a mixture of

14% **2b** and 86% of the thermally generated product identified as **1b**.

When **1a** was allowed to react with aqueous sodium acetate, *anti*-α-acetoxyacetophenone oxime (**2c**) was isolated. The nmr spectrum ($CDCl_3$) of **2c** showed a two-proton singlet at δ 4.97 and a three-proton singlet at δ 1.95. The corresponding peaks for the syn isomer **1c** (prepared as in eq 2) are δ 5.30 and 2.00.[3] Thermal isomerization of **2c** in



(2)

a manner analogous to that of **2b** resulted in a mixture containing 20% **2c** and 80% of the thermally generated product identified as **1c**.[9]

From the above results, it appears that the preparation of α-substituted oximes from the corresponding α-bromo oxime can be readily achieved with oxygen, nitrogen, and sulfur nucleophiles. The anti isomers can be produced directly from the *syn*-α-bromo oxime (eq 1) while the syn isomers can be prepared by first protecting the oxime function (eq 2). The sodium borohydride reduction of α-halo oximes may prove to be a generally useful synthetic route to thermally unstable anti alkyl aryl ketoximes.

Experimental Section

All melting points are uncorrected. Nmr spectra were obtained on Varian A-60 or A-60A spectrometers. Uv spectra were obtained on a Cary 15 instrument.

***anti*-Acetophenone Oxime (2d).** A 1.0-g (4.7 mmol) portion of **1a** dissolved in 10 ml of CH_3CN was added to a stirred solution of 177 mg (4.7 mmol) of $NaBH_4$ in 60 ml of water and 20 ml of CH_3CN at room temperature. Rapid evolution of a gas occurred but ceased within a few minutes. The pH dropped from 8 to 6 during this period. After 5 min the reaction mixture was extracted with $CHCl_3$ to give 624 mg of white solid which contained 90% *anti*- and 10% *syn*-acetophenone oxime as measured by nmr. This material was crystallized from $CHCl_3$–petroleum ether (bp 30–60°): mp 81–83°; nmr ($CDCl_3$) δ 9.7 (1 H, broad), 7.3–7.7 (5 H, m), 2.20 (3 H, s); uv λ_{max} (EtOH) 235 nm (log ε 3.86), λ_{max} (hexane) 231 nm (log ε 3.89).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.89; H, 6.72; N, 10.30.

Thermal Isomerization of 2d. A 500-mg portion of **2d** was dissolved in chlorobenzene and refluxed at 132°. An nmr analysis showed that the equilibrium mixture consisted of 5% **2d** and 95% *syn*-acetophenone oxime. This material was crystallized from petroleum ether, mp 58.5–59.5°, mmp with *syn*-acetophenone oxime 59.5–60.5°.

Beckmann Rearrangement of 2d. To a stirred suspension of 242 mg (1.16 mmol) of PCl_5 in 5 ml of benzene was added 157 mg (1.16 mmol) of **2d** dissolved in 5 ml of benzene. After 1.0 hr at room temperature, the reaction mixture was combined with 10 ml of benzene in a separatory funnel. Water was added and the mixture was shaken well. After extractions with 10% K_2CO_3 and water, the benzene portion gave 82 mg of white solid. A $CHCl_3$ extraction of the aqueous portion gave an additional 63 mg of white solid. An nmr analysis indicated that 80% of the recovered 145 mg of material was *N*-methylbenzamide. The remaining 20% was acetanilide.

Borohydride Reduction of 1a in Ethanol and Dimethoxyethane (DME). The procedure followed here was similar to that for the aqueous CH_3CN reaction described above except that ethanol or DME were used as solvents. With DME the reaction mixture was heterogeneous owing to the low solubility of $NaBH_4$ in that solvent. The work-up for both solvents consisted of adding the reaction mixture to water and extracting with $CHCl_3$. The major product obtained in each solvent was identified by nmr as *anti*-acetophenone oxime.

Stoichiometry of the Borohydride Reduction of 1a. The reductions described above for aqueous CH_3CN, EtOH, and DME solvents were carried out on a small scale with accurately weighed reagents. The borohydride was assayed by an iodometric procedure[10] and found to be approximately 100% pure. An aqueous solution of $NaBH_4$ at pH 8 showed no deterioration after 5 min at room temperature. The ratio of materials obtained by extraction of the reaction mixtures was determined by nmr. When 1.0 mol of $NaBH_4$ was used, the yield of acetophenone oxime was greater than 97%. When 0.5 mol of $NaBH_4$ was used, the yield ranged from 41 to 52%. These yields are based on the recovered mixture of starting material **1a** and products, which was typically about 95% of the theoretical amount.

Control Reaction of $NaBH_4$ with *syn*-Acetophenone Oxime. A 190-mg (1.4 mmol) portion of *syn*-acetophenone oxime in 3 ml of CH_3CN was added to 53 mg (1.4 mmol) of $NaBH_4$ dissolved in a mixture of 20 ml of water and 7 ml of CH_3CN. After 30 min at room temperature, $CHCl_3$ extraction gave 183 mg of material identified by nmr as recovered *syn*-acetophenone oxime.

***anti*-α-(*p*-Tolylthio)acetophenone Oxime (2b).** The solvents used in the preparation of **2b** were deoxygenated by bringing to reflux and cooling under a stream of nitrogen. A solution of *p*-tolyl thiolate was prepared by adding 100 ml of an ethanolic solution containing 6.2 g (0.05 mol) of *p*-toluenethiol to a solution containing 0.05 mol of NaOH in 300 ml of water and 50 ml of ethanol. This slightly turbid solution was stirred under a stream of nitrogen while 2.14 g (0.01 mol) of *syn*-α-bromoacetophenone oxime (**1a**) in 50 ml of ethanol was added. After a few minutes at room temperature, the resulting solution (very turbid) was extracted with $CHCl_3$ to give 2.4 g of an oil which solidified when the last traces of solvent were removed. Crystallization from CCl_4–petroleum ether gave colorless needles: mp 84.0–85.0°; nmr ($CDCl_3$) δ 8.5 (1 H, broad), 7.0–7.5 (9 H, m), 3.90 (2 H, s), 2.28 (3 H, s).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 69.99; H, 5.88; N, 5.45; S, 12.47. Found: C, 70.04; H, 5.92; N, 5.42; S, 12.35.

Thermal Isomerization of 2b. A 100-mg portion of **2b** was dissolved in $CDCl_3$, placed in a sealed nmr tube, and heated at 100° until nmr analysis showed no further change. The equilibrium mixture consisted of 14% **2b** and 86% **1b**. The mixture was crystallized from hexane, mp 83.5–84.0°, mmp with **1b** 83.5–84.5°.

***anti*-α-Acetoxyacetophenone Oxime (2c).** To a stirred solution of 14 g (0.1 mol) of sodium acetate trihydrate in 200 ml of water and 50 ml of CH_3CN was added 2 g (0.009 mol) of **1a** in 40 ml of CH_3CN. After 1 hr at room temperature, the reaction mixture was extracted with $CHCl_3$ to give 1.7 g of an oil which was crystallized from $CHCl_3$–petroleum ether: mp 47.5–49.5°; nmr ($CDCl_3$) δ 8.4 (1 H, broad), 7.3–7.7 (5 H, m), 4.97 (2 H, s), 1.95 (3 H, s).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.97; H, 5.78; N, 7.21.

Thermal Isomerization of 2c. A 63-mg portion of **2c** was subjected to conditions similar to **2b** described above. The equilibrium mixture contained 20% **2c** and 80% **1c**. The isomerization product could not be crystallized but had an nmr spectrum identical with that of **1c**.

***syn*-α-Bromoacetophenone Oxime Ketal (3a).** A solution of 1.0 g (4.68 mmol) of **1a**, 2.44 g (23.4 mmol) of 2,2-dimethoxypropane, 45 mg (0.23 mmol) of *p*-toluenesulfonic acid monohydrate, and 20 ml of CH_2Cl_2 was refluxed overnight. The solution was extracted with 1 *M* $NaHCO_3$ and the solvent was removed to give 1.22 g of an oil, nmr ($CDCl_3$) δ 7.3–7.85 (5 H, m), 4.37 (2 H, s), 3.33 (3 H, s), 1.57 (6 H, s).

***syn*-α-(*p*-Tolylthio)acetophenone Oxime Ketal (3b).** *p*-Toluenethiol (0.54 g, 4.34 mmol) was dissolved in 50 ml of deoxygen-

ated EtOH, and 2.0 ml of an aqueous 2.08 *M* NaOH solution was added. To this slightly turbid solution was added 0.62 g (2.17 mmol) of **3a** in 5 ml of EtOH. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in ether and extracted with 10% K_2CO_3 solution. Removal of the ether gave 0.61 g of an oil, nmr ($CDCl_3$) δ 7.0-7.7 (9 H, m), 4.12 (2 H, s), 3.20 (3 H, s), 2.30 (3 H, s), 1.42 (6 H, s).

syn-α-(*p*-**Tolylthio)acetophenone Oxime (1b).** A solution of 0.61 g of **3b** in 10 ml of CH_3CN was added to a mixture of 100 ml of aqueous 0.1 *M* HCl and 40 ml of CH_3CN and was stirred at room temperature for 30 min. Extraction of the heterogeneous reaction mixture with $CHCl_3$ gave 0.49 g of an oil which was crystallized from hexane: mp 84.0-85.0°; mmp with **2b** 61.5-66.0°; nmr ($CDCl_3$) δ 8.9 (1 H, broad), 6.9-7.65 (9 H, m), 4.17 (2 H, s), 2.28 (3 H, s).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 69.99; H, 5.88; N, 5.45; S, 12.47. Found: C, 70.08; H, 5.88; N, 5.47; S, 12.47.

syn-α-**Acetoxyacetophenone Oxime Ketal (3c).** A heterogeneous mixture containing 0.6 g (2.1 mmol) of **3a**, 1.0 g (7.35 mmol) of sodium acetate trihydrate, and 70 ml of CH_3CN was refluxed overnight. The reaction mixture was cooled and filtered, and the solvent was removed from the filtrate. The residue was taken up in ether and extracted with bicarbonate solution. The ether was removed to give 0.51 g of an oil, nmr ($CDCl_3$) δ 7.3-7.75 (5 H, m), 5.26 (2 H, s), 3.28 (3 H, s), 1.97 (3 H, s), 1.53 (6 H, s).

syn-α-**Acetoxyacetophenone Oxime (1c).** Removal of the ketal group was similar to the procedure for **1b**. Work-up gave 380 mg of an oil which could not be crystallized, nmr ($CDCl_3$) δ 9.8 (1 H, broad), 7.2-7.7 (5 H, m), 5.30 (2 H, s), 2.00 (3 H, s).

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Registry No.—**1a**, 17082-13-2; **1b**, 50314-81-3; **1c**, 50314-82-4; **1d**, 10341-75-0; **2b**, 50314-84-6; **2c**, 50314-85-7; **2d**, 50314-86-8; **3a**, 50314-87-9; **3b**, 50314-88-0; **3c**, 50314-89-1.

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(2) Throughout this article, syn refers to the isomer having the alkyl group cis to the oxime oxygen; anti refers to the isomer having the alkyl group trans to the oxime oxygen.
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