Nucleophilic Substitution Reactions of Phenacyl Bromide Oxime: Effect of the Solvent and the Basicity of the Nucleophile

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In the course of our recent work in the design, synthesis, and characterization of novel inhibitors for one of the catecholamine biosynthesizing enzymes, we were interested in the synthesis of *anti*-*O*-ethyl *S*-[2-(hydroxyimino)-2-phenylethyl] carbonodithioic acid ester (**2a**) which was a precursor for one of our target molecules. We found that **2a** was a known compound and the detailed synthesis was published.[1] In the published procedure it was mentioned that the reaction of phenacyl bromide oxime (**1a**) with potassium *O*-ethyl xanthate in acetone at room temperature for 4 h gives the *anti* isomer **2a** as the major product. In our trial experiments we were getting the extreme opposite results i.e. 10–20% *anti* and 90–80% *syn* even under exactly the same conditions. Similarly, all the previous studies[2–6] have reported that the original *syn* configuration of the oxime is converted predominantly to the thermodynamically less stable *anti* products regardless of the nature of the solvent or the nucleophile. In order to resolve this apparent discrepancy we have carried out a systematic study of the reaction.

The reaction of phenacyl bromide oxime (**1a**) with potassium *O*-ethyl xanthate in dry acetone produces two products at room temperature (24 °C). The ^{1}H- and ^{13}C-NMR analysis of the unresolved reaction products revealed that they were a mixture of *anti* and *syn* isomers of the expected compound (**2a** and **3a**) with ratios ranging from 20:80 to 10:90, respectively, depending on the concentrations of the reactants (Scheme 1 and Table 1). When the reaction was carried out in dry acetonitrile, a similar product distribution was observed. On the other hand, in methanol the product ratio changed drastically, producing a ratio of about 60:40 *anti* and *syn* isomers, respectively. Furthermore, the inclusion of 4% water in the methanol reaction medium increased the dominance of the *anti* isomer. Inclusion of the same amount of water in the acetone reaction medium completely reversed the isomer distribution from that of the anhydrous conditions and yielded the *anti* product predominantly (Table 1). However, the reaction of piperidine and the sodium salt of thiophenate with phenacyl bromide oxime in both methanol and acetone under identical reaction conditions yielded the corresponding *anti* isomers (**2b** and **2c**) predominantly as previously reported[2,5] (Table 1). In addition, stirring of a mixture of **2a** and **3a** (81:19) in dry acetone in the presence of 1.3 equiv of potassium

Scheme 1

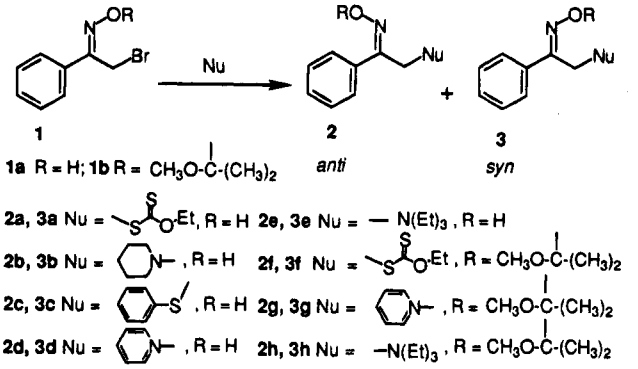

Table 1. Product Distribution of the Nucleophilic Substitution Reactions of Phenacyl Oxime Derivatives under Various Conditions[a]

nucleophile	solvent[b]	**1a** (mM)	*syn*:*anti*[c] (3:2)
xanthate	acetone	187	82:18
xanthate	acetone	23	89:11
xanthate	acetonitrile	292	78:22
xanthate	acetonitrile	117	90:10
xanthate	acetonitrile	23	93:07
xanthate	acetonitrile	23	93:07
xanthate	methanol	334	27:73
xanthate	methanol	234	40:60
xanthate	methanol	126	30:70
xanthate	methanol	27	42:58
xanthate	methanol	16	40:60
xanthate	96% methanol 4% H_2O	23	06:94
xanthate	96% acetone 4% H_2O	23	23:77
xanthate	acetone (0 °C[d])	195	95:05
xanthate	acetone (35 °C[d])	195	95:05
xanthate	MeOH + 4% H_2O (0 °C[d])	195	12:88
xanthate	MeOH + 4% H_2O (35 °C[d])	195	07:93
piperidine	acetone	234	20:80
piperidine	acetone	234	32:68
piperidine	acetone	21	18:82
piperidine	acetone	21	18:82
thiophenate	methanol	47	09:91
thiophenate	acetone	47	12:88
pyridine	acetone	X[e]	10–30:90–70[e]
triethylamine	acetone	X[e]	10:90[e]

[a] All the reactions were carried out at room temperature (24 ± 2 °C) except where stated otherwise. [b] All solvents used were purified and dried. [c] Isomer ratios were determined by ^{1}H-NMR integration of the corresponding fully resolved signals (due to the sensitivity limits of ^{1}H-NMR the accuracy of these numbers are in the range of ±10%). The isomer peak identification always places the *anti* isomer upfield of the *syn*, as stated in the literature.[7] [d] These experiments were carried out to examine the effect on the variability of the product distribution due to the small variations of room temperature. The results indicate that the variation is insignificant within the limits of experimental error. [e] These represent the results of several reactions.

O-ethyl xanthate under the identical reaction conditions revealed no significant isomerization (recovered **2a** to **3a** 80:20) suggesting that the predominant formation of the *syn* isomer with xanthate is not due to the isomerization of a possible original *anti* product to *syn* under the reaction conditions. Therefore, in contrast to previous reports,[2–6] these results clearly demonstrate that the nucleophilic substitution reactions of **1a** may proceed through different pathways that depend on the nature of the nucleophile, the reaction conditions, and nature of the solvent (especially the purity and the water content) and produce different isomer ratios.

The reaction of pyridine or triethylamine with **1a** in acetone quantitatively produces stable, crystalline phen-

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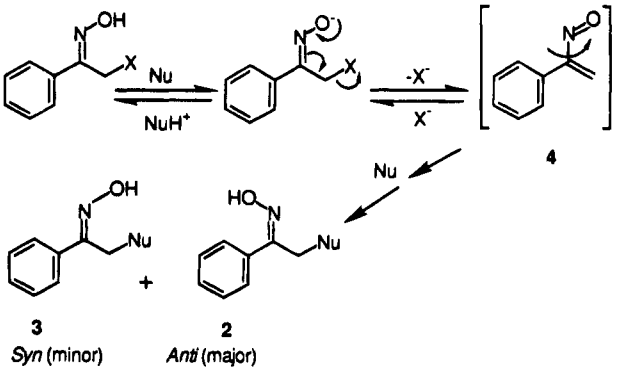
acyl pyridinium oxime (**2d** and **3d**) and phenacyl triethylammonium oxime (**2e** and **3e**), respectively. The structures of the corresponding products were confirmed by ^{1}H- and ^{13}C-NMR spectroscopy as predominantly *anti*, just as previous work indicates for nitrogen-containing nucleophiles (related quaternary ammonium salts of bromoacetophenone are known in the literature,[8,9] and the pyridinium oxime itself has been identified[8]). An unusual feature of these two compounds is that both react slowly (16 h) with xanthate in methanol to yield **2a** and **3a** in an isomer ratio of 9:1 (*anti:syn*), which is unprecedented to our knowledge for other quaternary ammonium compounds. For example, the corresponding keto compounds, phenacylpyridinium and phenacyltriethylammonium bromide salts, do not react with xanthate to a significant extent even under prolonged reaction times (data not shown). Therefore, it is clear that the oxime functionality of the above compounds plays an important role in their nucleophilic substitution reactions.

Previous kinetic studies of the S_N1 solvolysis reaction of phenacyl bromide oxime in aqueous solution by Smith *et al.*[3] have suggested that the abstraction of the proton from the oxime hydroxyl group is the initial step of the S_N1 pathway. Therefore, the nucleophilic substitution reactions of hydroxyl-blocked derivatives of **1a** should only undergo S_N2 type reactions and should retain the original (*syn*) configuration of the oxime. The hydroxyl-blocked oxime **1b** (*syn*) was found to react readily with xanthate under standard reaction conditions to yield pure *syn* product (**3f**) as expected. This compound **1b** was also found to react with both triethylamine and pyridine producing the respective salts with 100% *syn* configuration (**3h** and **3g**). However, both hydroxyl-blocked quaternary ammonium salts (**3h** and **3g**) were unreactive toward xanthate confirming that the triethylammonium and pyridinium groups of these molecules could not be replaced by an S_N2 type mechanism, and the S_N1 type mechanism could only be operative when the acidic hydrogen of the oxime functionality is removable.

The above results clearly demonstrate that the nucleophilic substitution reactions of phenacyl oxime derivatives undergo both S_N1 and S_N2 reactions depending on the nature of the nucleophile, leaving group, solvent, and the reaction conditions. The reaction between **1a** and weakly basic xanthate (the pK_a of xanthic acid was determined to be 1.6 in aqueous medium) favors an S_N2 type mechanism in aprotic solvents leading to the predominant production of the uncommon *syn* isomer. This must at least partly be due to the inability of the xanthate anion to abstract the proton of the hydroxyl group of the oxime (although the exact pK_a for this particular compound is unavailable, the pK_a range of most α-chloro ketoximes has been cited as 3–4[10]) efficiently under the reaction conditions. However, it should be noted that the S_N1 pathway can be predominant even with weakly basic nucleophiles such as xanthate depending on the nature of the solvent and the reaction conditions. On the other hand, the amine-containing and other strongly basic (e.g. thiophenate anion) nucleophiles which are capable of efficient abstraction of the proton of the oxime functionality undergo preferential S_N1 reactions producing predominantly the *anti* isomer, regardless of the nature of the solvent or the reaction conditions, as reported in the literature. In the nucleophilic substitution reactions of phenacylpyridinium and -triethylammonium oximes (**2d**, **3d**, **2e**, and **3e**), only the S_N1 type mechanism is operative even with the weakly basic xanthate nucleophile mainly due to the poor leaving ability of the leaving group.

Scheme 2



The above results confirm that regardless of the original configuration of the oximes or the nature of the nucleophile (at least for the nucleophiles tested), the S_N1 pathway always yields the *anti* oxime as the predominant product. For example, the S_N1 reactions of both triethylammonium and pyridinium phenacyl oximes (90% *anti* (**2e** and **2d**)) as well as **1a** (100% *syn*) with xanthate yield predominantly the corresponding *anti* oximes (see above). These findings are in agreement with the previous proposal that α-nitrosostyrene (**4**)[2,10,11] is an intermediate in the S_N1 reactions of phenacyl oxime derivatives (Scheme 2). In order to gain insight into the mechanistic details of the above reaction we have explored the energetics of the nitrosostyrene intermediate by semiempirical MNDO/AM1 calculations. These calculations[12] suggest that the *s-cis* conformation of α-nitrosostyrene is more stable by 0.3 kcal/mol than the *s-trans*, but with a low rotational barrier of 1.8 kcal/mol, suggesting that the predominant formation of the *anti* product could not be a ground state effect but must be due to reaction pathway dynamics and the relative stabilities of the *syn* and *anti* transition states.

The above findings are consistent with the proposal of Smith and Kaiser that the predominant formation of the *anti* product from morpholine-like nucleophiles is due to the high reactivity of the *s-trans* conformation of nitrosostyrene in comparison to the *s-cis* form.[3] This proposal has been modeled by using methoxide as a simple nucleophile since its reactivity is similar to that of xanthate (and thiophenate). The calculations demonstrate that both *syn* and *anti* 1-phenyl-2-methoxyethanone oxime anions were found to have 1.44 Å CH_2—O bond lengths, with heats of formation of −56.15 and −55.57 kcal/mol, respectively, suggesting the *syn* product is more stable by 0.58 kcal/mol which is in agreement with the previous experimental observations for other nucleophiles.[2-6] The transition state geometries of *syn* (or *s-cis*) and *anti* (or *s-trans*) isomers were located

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(12) It should be emphasized that the semiempirical calculations of similar systems (e.g. 1,3-butadiene) are not always accurate (we thank one of the reviewers for pointing this out). For example see Rayez, J. C.; Dannenberg, J. J. *Chem. Phys. Lett.* **1976**, *41*, 492–496. However, even though the values of the relative stabilities of these isomers may not be accurate the observed low rotational barrier is expected.

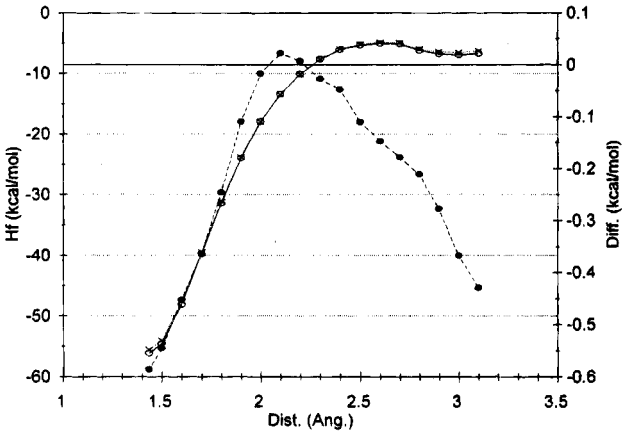

Figure 1. The *syn* and *anti* oxime anion products of the reaction between α-nitrosostyrene and methoxide were minimized (all parameters) for various fixed CH_2—O distances as detailed in Experimental Section using the AM1 parameter set. The heats of formation for both the *syn* (○) and *anti* (×) isomers are plotted along with the difference [*syn* − *anti*] (●) against CH_2—O distances.

approximately by minimizing structures for fixed CH_2—O bond lengths in the range of 1.5 to 3.1 Å and were refined and verified according to the criteria given in the Experimental Section. The transition states CH_2—O distances were found to be 2.62 Å (−5.02 kcal/mol) for the *s-cis* (*syn*) isomer and 2.63 Å (−4.89 kcal/mol) for the *s-trans* (*anti*) isomer. The stationary state for the reactants, α-nitrosostyrene and methoxide, probably an ion−dipole complex,[13] was found at a CH_2—O distance of 3.00 Å (−6.93 kcal/mol) for the *s-cis* isomer and 2.97 Å (−6.57 kcal/mol) for the *s-trans* isomer. In addition, the data presented in Figure 1 demonstrate that the difference in the stabilities between *s-cis* and *s-trans* intermediates decreases with decreasing CH_2—O distance from 3.1 Å up to about 2.1 Å and then increases until the equilibrium distance is reached, suggesting that the approach of the nucleophile stabilizes the *s-trans* configuration relative to the *s-cis* configuration in the initial stages of bond formation, including the transition state. The calculated activation energies were 1.91 and 1.68 kcal/mol for *s-cis* and *s-trans* isomers, respectively, suggesting that the *s-trans* isomer is more reactive than the *s-cis* isomer in agreement with the proposal of Kaiser and Smith.[3] Similar results were also obtained by using methanethiolate as the model nucleophile. However, the refinement of the approximate transition state was not possible due to the extremely low activation energies of the reaction. In contrast, when NH_3 was used as the nucleophile *s-cis* was found to be more reactive than the *s-trans* presumably due to the stabilization of the *s-cis* transition state due to intramolecular electrostatic and/or H-bonding effects suggesting that the above model may only be satisfactory for anionic nucleophiles.

Similar calculations for deprotonated **2a** and **3a** also predict that the *syn* isomer is thermodynamically more stable than the corresponding *anti* isomer. An experimental proof for this comes from our observation that a crude (contaminated with small amounts of potassium *O*-ethyl xanthate) sample of **2a** was completely converted to **3a** upon long term storage at room temperature (data not shown). Therefore, the S_N1 reactions of phenacyl bromide oxime predominantly produce the *anti* isomer as a kinetically controlled product. The predicted high reactivity of *s-trans* in comparison to *s-cis* α-nitrosostyrene is in excellent agreement with this notion. However, it should be emphasized that the final isomer ratio should be a function of not only the relative reactivities and populations of the two isomers of α-nitrosostyrene, but also of various solvent interactions which are not accounted for in the calculations. In addition, although rotation about the C—N bond during the course of the reaction has not been explored in our calculations, the predominant formation of the thermodynamically less stable product suggests that significant isomerization should not take place after initiation of the reaction.

Taken together, our results conclusively establish that phenacyl bromide oxime can undergo both S_N1 and S_N2 reactions depending on the nature of the nucleophile, the solvent, and the reaction conditions. While strongly basic nucleophiles such as amines and thiolate anions favor the S_N1 pathway in all solvents, weakly basic nucleophiles such as xanthate prefer the S_N1 pathway *only* in protic solvents. The experimental results demonstrate that the S_N1 pathway always predominantly produces the thermodynamically less stable *anti* isomer. These results are supported by theoretical calculations which predict that *s-trans* α-nitrosostyrene is more reactive than *s-cis*. These observations are in agreement with all the previous reports except one, where it has been reported that the reaction between phenacyl bromide oxime and potassium *O*-ethyl xanthate in acetone produces *anti* as the major isomer. On the basis of our results we believe this anomaly is probably due to the presence of water in the solvent.

Experimental Section

General Procedures. All melting points were determined using a Mel-Temp II apparatus and are uncorrected. ^1H- and ^{13}C-NMR spectra were recorded using a Varian XL-300 (300 MHz) instrument against a TMS standard. All the solvents were purified and dried according to the standard procedures. All the reactions were carried out at room temperature (24 °C) unless otherwise stated.

Semiempirical MOPAC Calculations. Restricted Hartree−Fock molecular orbital calculations were carried out using MOPAC 6.0. The AM1 parameter set[14] was employed with default options except that the keywords SCFCRT = 1e−12, GNORM = 0.01, and PRECISE were added to increase precision. All geometries were optimized using the standard BFGS method.[15] The rotational barriers for the α-nitrosostyrene intermediate were estimated by minimizing the energy for various (15° increments) fixed CH_2=C—N=O dihedral angles. The rotational transition state for the lower of the two barriers was isolated using the eigenvector following routine[16] and identified by having exactly one negative vibration in a force calculation on the obtained geometry.[17] The *syn* and *anti* oxime anion products of the reaction between α-nitrosostyrene and model nucleophiles were minimized (all parameters) using the AM1 parameter set. For the approximate estimation of the transition state geometries, the product structures were minimized for various fixed CH_2—Nu distances. The transition states were refined and verified by the same method and criteria as used for the rotational barriers.

2-Bromo-1-phenylethanone Oxime (1a). This was prepared by the method of Korten and Scholl,[18] with the correction

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that the products are chloro and bromo *syn* compounds, not *syn* and *anti* as originally identified.[7] ^{1}H-NMR (DMSO-d_6) δ: 7.39–7.73 (5H, m), 4.55 (2H, s), 4.72 (trace, s; due to the presence of a trace of the corresponding chloro derivative; see ref 7).

2-Bromo-1-phenylethanone Oxime *O*-(1-Methoxy-1-methylethyl) Ether (1b). This compound was prepared by the method of Smith and Kaiser.[4] ^{1}H-NMR (DMSO-d_6) δ: 7.41–7.77 (5H, m), 4.72 (trace, s; trace of *syn* chloro), 4.55 (2H, s; *syn*), 3.20 (3H, s), 1.51 (6H, s).

***O*-Ethyl *S*-[2-(Hydroxyimino)-2-phenylethyl] Carbonodithioic Acid Ester (2a and 3a).** All the reactions were carried out in the scale of 0.25 or 0.50 g (**1a**). The desired concentrations of the oxime were achieved by varying the amount of the solvent (Table 1). In a typical reaction, 0.25 g (1.17 mmol) of phenacyl bromide oxime was dissolved in one half of the solvent and 0.21 g (1.31 mmol) of potassium *O*-ethyl xanthate in the other half of the solvent was added with stirring. The reaction was allowed to stir for 2 h, filtered and evaporated to dryness *in vacuo*. The residue was taken up in ether and washed with 3 × 100 mL H_2O. The ether layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to yield a viscous oil of which the color ranged from yellow to dark green depending on isomer composition (Table 1). ^{1}H-NMR (DMSO-d_6) δ: 7.33–7.68 (5H, m), 4.59 (2H, J = 7.1 Hz, q), 4.47 (s, SCH_2 *syn* isomer), 4.34 (s, SCH_2 *anti* isomer), 1.31 (3H, J = 7.1 Hz, t).

1-Phenyl-2-(1-piperidinyl)ethanone Oxime (2b and 3b). A mixture of 0.25 g (1.17 mmol) of **1a** and 0.26 mL (2.58 mmol) of piperidine in acetone was stirred for 4 h. The precipitate was removed by filtration and the solvent was evaporated *in vacuo* to give a solid material. This was taken up in ether, washed with 3 × 100 mL H_2O, and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to obtain 0.60 g of an oil. This was recrystallized from chloroform/ethanol to give 0.15 g (60% yield) of product. ^{1}H-NMR (DMSO-d_6) δ: 7.30–7.65 (5H, m), 3.74 (s, NCH_2 *syn* isomer), 3.33 (s, NCH_2 *anti* isomer), 1.3–2.7 (10H, m).

1-Phenyl-2-thiophenoxyethanone Oxime (2c and 3c). A mixture of 0.16 g (1.25 mmol) of sodium thiophenate in 10 mL of methanol [or acetone (see Table 1)] and 0.25 g (1.17 mmol) of **1a** in 10 mL was stirred for 2 h and the solvent was evaporated *in vacuo*. The product was taken up in ether and washed with 3 × 100 mL of H_2O, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* at room temperature to give 0.26 g white solid (91% yield) of mp 82 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.03–7.58 (10H, m), 4.12 (s, SCH_2 *syn* isomer), 3.84 (s, SCH_2 *anti* isomer). Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.11; H, 5.39; N, 5.76; O, 6.58; S, 13.18. Found: C, 68.87; H, 5.43; N, 5.77.

1-(2-(Hydroxyimino)-2-phenylethyl)pyridinium Bromide Salt (2d and 3d). A solution of 0.50 g (2.34 mmol) of **1a** in 30 mL of dry methanol was treated with 4 mL (50 mmol) of pyridine. The solvent was evaporated to dryness *in vacuo*. The product was washed several times with ether to give 0.57 g of white solid (84% yield) of mp 207 °C. ^{1}H-NMR (DMSO-d_6) δ: 9.16 (2H, J = 5.6 Hz, d), 8.65 (1H, J = 7.8 Hz, t), 8.20 (2H, J = 7.1 Hz, t), 7.43–7.69 (5H, m), 6.03 (s, N^+CH_2 *syn* isomer), 5.91 (s, N^+CH_2 *anti* isomer). Anal. Calcd for $C_{13}H_{13}BrN_2O$: C, 53.26; H, 4.47; N, 9.56; Br, 27.26; O, 5.46. Found: C, 53.50; H, 4.62; N, 9.68.

***N,N,N*-Triethyl-2-(hydroxyimino)-2-phenylethanaminium Bromide Salt (2e and 3e).** A solution of 0.50 g (2.34 mmol) of **1a** in 30 mL of dry acetone was treated with 4 mL (30 mmol) of triethylamine. The precipitate was filtered and washed with acetone to give 0.47 g of white solid (64% yield) of mp 144–5 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.44–7.72 (5H, m), 4.59 (s, N^+CH_2 *syn* isomer), 4.40 (s, N^+CH_2 *anti* isomer), 3.20 (6H, J = 7.1 Hz, q), 1.09 (9H, J = 7.1 Hz, t). Anal. Calcd for $C_{14}H_{23}BrN_2O$: C, 53.34; H, 7.35; N, 8.89; Br, 25.35; O, 5.08. Found: C, 53.56; H, 7.18; N, 8.97.

***O*-Ethyl *S*-[2-[*N*-(1-methoxy-1-methylethoxy)imino]-2-phenylethyl] Carbonodithioic Acid Ester (3f).** A mixture of 0.45 g (1.57 mmol) of **1b** in 5 mL of methanol and 0.30 g (1.87 mmol) of potassium *O*-ethyl xanthate in 10 mL of ethanol was stirred overnight. Methanol was evaporated *in vacuo*, the residue was taken up in ether, washed with 3 × 100 mL of H_2O, and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to give 0.49 g (95% yield) of a yellow oil. ^{1}H-NMR (DMSO-d_6) δ: 7.42–7.70 (5H, m), 4.59 (2H, J = 7.1 Hz, q), 4.49 (2H, s), 3.17 (3H, s), 1.47 (6H, s), 1.28 (3H, J = 7.1 Hz, t). Anal. Calcd for $C_{15}H_{21}NO_3S_2$: C, 55.02; H, 6.46; N, 4.28; O, 14.66; S, 19.58. Found: C, 55.17; H, 6.50; N, 4.31.

1-[2-[*N*-(1-Methoxy-1-methylethoxy)imino]-2-phenylethyl]pyridinium Bromide Salt (3g). A mixture of 0.20 g (0.70 mmol) of **1b** and 4 mL (50 mmol) of pyridine in 20 mL of methanol was stirred overnight. The solvent and excess pyridine were evaporated *in vacuo* at room temperature to give 0.24 g of a clear oil (92% yield.) ^{1}H-NMR (DMSO-d_6) δ: 7.33–9.30 (10H, m), 6.16 (2H, s), 3.01 (3H, s), 1.36 (6H, s). ^{1}H-NMR spectra of this compound contained a small amount of a minor isomer with a methylene singlet at 6.02 ppm. This is believed to be a second orientation of the blocking group with respect to the methylene, i.e. a blocking group rotamer. [Accurate analytical data could not be obtained due to partial deblocking of this compound at room temperature.]

***N,N,N*-Triethyl-2-[*N*-(1-methoxy-1-methylethoxy)imino]-2-phenylethanaminium Bromide Salt (3h).** A solution of 0.20 g (0.7 mmol) of **1b** in 20 mL of methanol and 4 mL (30 mmol) of triethylamine was stirred overnight. The solvent and excess triethylamine were evaporated *in vacuo* to give 0.24 g of a clear oil (89% yield). ^{1}H-NMR (DMSO-d_6) δ: 7.40–7.77 (5H, m), 4.65 (2H, s), 3.19 (9H, m), 1.50 (6H, s), 1.17 (9H, J = 7.1 Hz, t). [Accurate analytical data could not be obtained due to partial deblocking of this compound at room temperature.]

Reaction of 2d/3d (a mixture of 90% 2d and 10% 3d) with Potassium *O*-Ethyl Xanthate. A solution of 0.29 g (0.99 mmol) of phenacylpyridinium oxime (**2d** and **3d**) and 0.20 g (1.25 mmol) of potassium *O*-ethyl xanthate in 30 mL methanol was stirred overnight. The solvent was evaporated *in vacuo*. The residue was taken up in ether, washed with 3 × 75 mL of H_2O, and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield 0.16 g (63% yield) of an oily product. ^{1}H-NMR analysis indicated this was a 90:10 mixture of **2a** and **3a**, respectively.

Reaction of 2e/3e (a mixture of 90% 2e and 10% 3e) with Potassium *O*-Ethyl Xanthate. A solution of 0.31 g (0.98 mmol) of phenacyltriethylammonium oxime (**2e** and **3e**) and 0.20 g (1.25 mmol) potassium *O*-ethyl xanthate in 30 mL methanol was stirred overnight at room temperature. The solvent was evaporated *in vacuo*. The residue was taken up in ether and washed with 3 × 75 mL of H_2O and dried over anhydrous $MgSO_4$, and the solvent was evaporated *in vacuo* to yield 0.15 g (59% yield) of an oily product. ^{1}H-NMR analysis indicated this was a 90:10 mixture of **2a** and **3a**, respectively.

Reaction of 3g with Potassium *O*-Ethyl Xanthate. A mixture of 0.24 g (0.84 mmol) of **3g** and 0.16 g (1.00 mmol) of potassium *O*-ethyl xanthate in 30 mL of methanol was stirred overnight. The solvent was evaporated *in vacuo* and ^{1}H-NMR analysis of the crude reaction mixture proved that no reaction occurred.

Reaction of 3h with Potassium *O*-Ethyl Xanthate. To a solution of 0.24 g (0.78 mmol) of **3h** in 30 mL of methanol was added 0.16 g (1.00 mmol) potassium *O*-ethyl xanthate (0.16 g), and the reaction was stirred overnight. The solvent was evaporated *in vacuo* and ^{1}H-NMR analysis of the crude reaction mixture proved that no reaction occurred.

1-(2-Oxo-2-phenylethyl)pyridinium Bromide Salt. A solution of 2.02 g (9.44 mmol) of phenacyl bromide in 30 mL dry acetone was treated with 3 mL (40 mmol) pyridine. After several minutes a white solid product precipitated. The solid was filtered and washed with acetone to obtain 2.40 g of white solid (85% yield) of mp 193 °C. ^{1}H-NMR (DMSO-d_6) δ: 9.01 (2H, J = 6.6 Hz, d), 8.74 (1H, J = 6.5 Hz, t), 8.29 (2H, J = 6.7 Hz, t), 8.05 (2H, J = 7.1 Hz, d), 7.79 (1H, J = 7.4 Hz, t), 7.66 (2H, J = 8.1 Hz, t), 6.52 (2H, s).

Supplementary Material Available: ^{13}C-NMR assignments for important compounds, ^{1}H-NMR spectra of **3g**, **3h**, and mixtures of **2a/3a**, and MOPAC 6.0 .ARC output files for minimized geometries and isolated transition states (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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