products for starting material (1) and methylated derivatives 2, 3, and 4. The results are given in Table I. When the reaction was run with *N*-lithio-*N*,*N*',*N*'-trimethylethylenediamine (LTMDA) by using our standard conditions,[2c] an oil was isolated in 85% yield, which contained 90% of the desired aldehyde 2, 8% of isomers 3 and 4, and 2% starting material (1). A similar reaction using benzene as the solvent (entry b) also failed to give the desired degree (>95%) of substitution at the 2-position. The use of lithium *N*-methylpiperazide (LNMP) as the amine component allowed for better regioselectivity, but incomplete metalation occurred (entries c and d).

In an attempt to find an α-amino alkoxide with the desired ortho-directing power, we examined the reaction with *N*-lithio-*N*,*N*',*N*'-trimethylhydrazine[8] (LTMH) as the amine component. Interestingly, LTMH did form an effective ortho-directing α-amino alkoxide of intermediate strength (entries e and f). When LTMH was the amine component, benzene the solvent, and phenyllithium[9] the base, a highly regioselective lithiation–methylation occurred in high yield (entry g). Phenyllithium also proved to be an effective base for metalations of LTMDA derived α-amino alkoxides. In toluene or benzene, a highly regioselective methylation occurred to give the desired 2-methyl-3-methoxybenzaldehyde (2) in high yield (entries h–j).

Apparently, the lower basicity of phenyllithium, as compared to *n*-butyllithium, is responsible for the increased regioselectivity. The use of phenyllithium as a base allowed us to solve the "*m*-anisaldehyde problem". It is likely that phenyllithium would be effective in other directed lithiation reactions, and its potential as a base should not be overlooked.[10]

Experimental Section

Reactions were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone ketyl prior to use. Benzene, toluene, *N*,*N*',*N*'-trimethylethylenediamine, *N*-methylpiperazine, and *N*,*N*',*N*'-trimethylhydrazine[8] were distilled from calcium hydride and stored over 3-Å molecular sieves under N_2.

Gas–liquid chromatography (GC) was performed on a Hewlett-Packard Model 5890A gas chromatograph equipped with a 30 m × 0.25 mm FSOT column packed with OV-101. Radial preparative-layer chromatography (radial PLC) was carried out by using a Chromatotron (Harrison Assoc., Palo Alto, CA).

Preparation of 2-Methyl-3-methoxybenzaldehyde from *m*-Anisaldehyde. General Procedure for the α-Amino Alkoxide Directed Lithiation Reactions. To a solution of 0.41 mL (3.2 mmol) of *N*,*N*',*N*'-trimethylethylenediamine in 8 mL of benzene was added 3.1 mmol of *n*-BuLi (2.3 M in hexane) dropwise with cooling (ice bath). After 15 min at room temperature, *m*-anisaldehyde (0.37 mL, 3.0 mmol) was added (0–5 °C) and the mixture was stirred at room temperature for 15 min. A solution of phenyllithium (4.5 mL, 9 mmol) in cyclohexane/ether[9] was added with cooling (ice bath). After the mixture was stirred at room temperature for 8 h, 8 mL of THF was added while the mixture was being cooled to −78 °C. Methyl iodide (1.1 mL, 18 mmol) was added slowly at −78 °C, the cooling bath was removed, and the mixture was allowed to come to room temperature (30 min). The mixture was poured into cold, vigorously stirred 10% HCl and extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give 510 mg of a dark oil. Purification by radial PLC (SiO_2, 5–20% EtOAc/hexanes) gave 410 mg (91%) of a light yellow oil. This oil consisted of 96% 3-methoxy-2-methylbenzaldehyde and 4% *m*-anisaldehyde as indicated by GC analysis.

Acknowledgment. We thank Larry Overman and Victor Snieckus for bringing the "*m*-anisaldehyde problem" to our attention.

(8) Trimethylhydrazine was prepared by a literature procedure, see: Class, J. B.; Aston, J. G.; Oakwood, T. S. *J. Am. Chem. Soc.* **1953**, *75*, 2937.

(9) Phenyllithium was purchased from Aldrich Chemical Co. as a 2.0 M solution in cyclohexane–ether.

(10) Phenyllithium is an effective base for the regioselective α-lithiation of certain 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines. Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1988**, *53*, 4437.

Dye-Sensitized Photooxygenation of the C=N Bond[1]

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Since the early 1970s, photooxygenations of a variety of compounds containing the C=N bond have been reported.[2-12] In some cases these reactions appear to use or-

(1) A preliminary account of this work was reported at the Pacific Conference on Chemistry and Spectroscopy, San Francisco, Oct 27, 1988.

(2) For a review of reactions of $^1O_2$ with nitrogen-containing heterocycles, see: George, M. V.; Bhat, V. *Chem. Rev.* **1979**, *79*, 447–478. Also useful is the review by Boyer: Boyer, J. H. *Chem. Rev.* **1980**, *80*, 495–561.

(3) (a) Imines undergo photooxygenation and photooxidative cleavage via reaction of the triplet state with triplet oxygen: Toshima, N.; Hirai, H. *Tetrahedron Lett.* **1970**, 433–436. (b) Schiff bases undergo cleavage of the C_α—C= single bond subsequent to photooxidative C_α—H cleavage by triplet oxygen: McCapra, F.; Burford, A. *J. Chem. Soc., Chem. Commun.* **1976**, 607–608. (c) N–H hydrazones react with oxygen in an ene reaction giving *C*-hydroperoxyazo adducts, thence fragmentation products; singlet oxygen is not required: Yao, H. C.; Resnick, P. *J. Org. Chem.* **1965**, *30*, 2832–2834. Lewis, G. E.; Spencer, G. I. *Aust. J. Chem.* **1975**, *28*, 1733–1739.

(4) (a) Benzophenone oxime, its methyl ether, and its conjugate base are all cleaved to benzophenone by $^1O_2$: Wamser, C. C.; Herring, J. W. *J. Org. Chem.* **1976**, *41*, 1476–1477. (b) Oximes and oxime ethers are, in general, inert or almost so to $^1O_2$. Acetone oxime shows marginal reactivity.[4a] Valerophenone oxime *O*-methyl ether does not react: Ito, Y.; Konishi, M.; Matsuura, T. *Photochem. Photobiol.* **1979**, *30*, 53–57. Cyclohexanone oxime, its methyl ether, and acetophenone oxime react very sluggishly with $^1O_2$: Chawla, H. M.; Hassner, A. *Tetrahedron Lett.* **1986**, *27*, 4619–4622. Chawla and Hassner also showed that oxime carbamates react with $^1O_2$ preferentially at the C—N center rather than the C=N center. The relative inertness of oximes to singlet oxygen is confirmed in the present study. *C*-Nitroso compounds (formally tautomeric with oximes and oxime ethers) have been shown to quench $^1O_2$, "...probably by an energy transfer mechanism": Singh, P.; Ullman, E. F. *J. Am. Chem. Soc.* **1976**, *98*, 3018–3019.

(5) Imidazoles give a variety of products depending on the substitution pattern. These reactions appear to begin by electrophilic addition (resembling the reaction of $^1O_2$ with enamines[6]) and/or by 1,4-cycloaddition: Wasserman, H. H.; Stiller, K.; Floyd, M. B. *Tetrahedron Lett.* **1968**, 3277–3280.

(6) (a) Foote, C. S.; Lin, J. W.-P. *Tetrahedron Lett.* **1968**, 3267–3270. Foote, C. S.; Dzakpasu, A. A.; Lin, J. W.-P. *Tetrahedron Lett.* **1975**, 1247–1250. (b) For a review, see: Schaap, A. P.; Zaklika, K. A. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic: New York, 1979; p 180.

(7) (a) Sydnones are proposed to react with $^1O_2$ by 1,3-cycloaddition with subsequent fragmentation: Bhat, V.; Dixit, V. M.; Ugarkar, B. G.; Trozzolo, A. M.; George, M. V. *J. Org. Chem.* **1979**, *44*, 2957–2961. (b) An azomethine imine was shown by the same workers to be cleaved by $^1O_2$ to the parent ketone. This reaction too might begin with 1,3-cycloaddition. (c) Aziridines, via their azomethine ylide forms, afford products with $^1O_2$ which can be rationalized by 1,3-cycloaddition followed by fragmentations: Bhat, V.; George, M. V. *J. Org. Chem.* **1979**, *44*, 3288–3292. Bhat, V.; George, M. V. *Tetrahedron Lett.* **1977**, 4133–4136. (d) Diazoalkanes are cleaved by $^1O_2$ to carbonyl compounds; in the presence of aldehydes, ozonides are also formed. The initial stage is probably 1,3-cycloaddition and/or electrophilic addition: Higley, D. P.; Murray, R. W. *J. Am. Chem. Soc.* **1974**, *96*, 3330–3332. Bethell, D.; McKeiver, R. *J. Chem. Soc., Perkin Trans. 2* **1977**, 327–333.

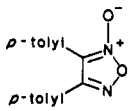
0022-3263/89/1954-3732$01.50/0

Table I. Products from the Dye-Sensitized Photooxygenation of Selected C=N Compounds[a]

type of compd	solvent/temp, °C	time, h	products
oximes[b]	CCl_4/25 or acetone-d_6/25	7–12	no reaction
O-trimethylsilyloximes ($ArC(R)=NOSiMe_3$)	CCl_4/25	7–9	no reaction
aldoximate ions ($ArCH=NO^-$)	CH_3OH/CH_3O^-/25	3	$ArCO_2CH_3$, $ArCO_2H$, ArCHO
ketoximate ions ($ArC(CH_3)=NO^-$)	CH_3OH/CH_3O^-/25	3	$ArC(CH_3)O$
nitronate ions[c] ($RCH=NO_2^-$)	D_2O/DMSO-d_6 (5:1)/25	2	no reaction
	D_2O/DMSO-d_6/CCl_4 (5:1:3)/25, with cetyltrimethylammonium bromide	2	RCHO
	CH_3OH/CH_3O^-/25	2	RCHO
O-trimethylsilylnitronates ($R_1R_2C=N(O)OSiMe_3$)	CCl_4/25	2	R_1R_2CO
hydrazones[d]	CCl_4 or CH_2Cl_2/25	22	no reaction
	CH_2Cl_2/−78	12–22	ArC(R)O
C-arylnitrones	See Table II.		

[a] See text for details. [b] See also ref 4. [c] See also ref 11. [d] See also ref 3c and 10.

Table II. Products from the Dye-Sensitized Photooxygenation of *C*-Arylnitrones[a]

entry	nitrone, $ArC(R_1)=N(R_2)O$: Ar, R_1, R_2	relative amounts of products: $ArCOR_1$	$ArC(R_1)=NOH$	other(s)
1	*p*-MeC_6H_4, H, Me	1.7	1.4	HCO_2H (1), HCONHOH[b]
2	*p*-$O_2NC_6H_4$, H, Me	3.5	1	HCO_2H (1), HCONHOH[b]
3	*p*-$Me_2NC_6H_4$, H, Me	all	none	HCONHOH[b]
4	*p*-MeC_6H_4, H, Me_2CH	1	2	CH_3COCH_3 (1.6), $(CH_3)_2C=NOH$ (0.14)
5	*p*-MeC_6H_4, Me, Me	2.6	1.2	HCO_2H (1), HCONHOH[b]
6	*p*-$O_2NC_6H_4$, Me, Me	all	none	HCONHOH[b]
7	PhCH=CH, H, Me	0.3	3	HCO_2H (1), HCONHOH[b] PhCHO (0.03), $PhCH=CHCO_2H$ (trace)
8	PhCH=CH, H, Me	no reaction in CD_3OD after 7 h[c]		
9	*p*-MeC_6H_4, H, Ph	10% conversion to *p*-tolualdehyde after 9 h at room temperature, 27% conversion after 9 h at −78 °C in CH_2Cl_2[d]		
10	Ph, H, *t*-Bu	6% conversion to benzaldehyde and 2-methyl-2-nitropropane after 6 h at room temperature; 18% conversion after 9 h at −78 °C in CH_2Cl_2[e]		
11		no reaction after 7 h		

[a] Reactions run at room temperature in $CCl_4/CDCl_3$ (3:1, v/v) with TPP sensitization unless otherwise specified. Qualitatively similar results were found for *C*-*p*-tolyl-*N*-methylnitrone in CH_2Cl_2 and in acetone at both room temperature and −78 °C. [b] This product was not quantified. [c] Both TPP and RB sensitization were tried. [d] *p*-Tolualdehyde and nitrobenzene were identified by ^1H NMR. The aldehyde was also formed in the control reactions (no TPP): 10–12% after 9 h at room temperature and 0–15% after 9 h at −78 °C. [e] Benzaldehyde was identified by ^1H NMR and by GLPC, 2-methyl-2-nitropropane by GLPC (SE-30 capillary column, 100–240 °C).

dinary triplet oxygen,[3] while in others, singlet oxygen ($^1O_2$) is required or strongly implicated.[4-12] Mechanistic inferences drawn from the singlet oxygen studies have often relied mainly on the identities of the products. Although plausibly based on analogy with the reactions of $^1O_2$ with alkenes,[13] dienes,[14] and amines,[15] the mechanisms of the reactions with C=N compounds remain speculative. A coherent overview is lacking.

We report here a survey of the reactions of singlet oxygen with several types of C=N-containing compounds. The results (see Tables I and II) indicate that strong electron donors attached to nitrogen greatly facilitate reaction. The products formed are, however, highly particular to substrate structure; moreover, reactivity can depend on solvent and temperature as well.

Our photooxygenations were carried out by using a 250-W sodium vapor lamp and the dye sensitizers tetraphenylporphyrin (TPP) or rose bengal (RB). Illuminated reaction solutions were stirred in an oxygen atmosphere, and reaction progress was monitored by TLC and ^1H NMR. All product identifications were confirmed by comparison (TLC, ^1H and ^{13}C NMR, IR) with authentic samples of known substances. The involvement of singlet

(8) Imidazolines give products that appear to arise from an ene reaction followed by tautomerization to a 1,2-bisenamine, then further reaction with $^1O_2$: Bhat, V.; George, M. V. *J. Org. Chem.* **1979**, *44*, 3288–3292.

(9) *N*-Phenylpyrazolines (cyclic five-membered hydrazones) react with $^1O_2$ to yield, principally, pyrazoles. Other products are also formed. Dual pathways using both singlet and triplet oxygen were invoked: Evans, N. A.; Leaver, I. H. *Aust. J. Chem.* **1974**, *27*, 1797–1803. Evans, N. A. *Aust. J. Chem.* **1975**, *28*, 433–437.

(10) (a) *N,N*-Dimethylhydrazones with C_α—H bonds react with $^1O_2$ at room temperature or −78 °C with net C=N cleavage to the parent ketone upon reductive workup. Evidence is given for an ene pathway via a *N*-hydroperoxy adduct: Friedrich, E.; Lutz, W.; Eichenauer, H.; Enders, D. *Synthesis* **1977**, 893–894. (b) Other N,N-disubstituted hydrazones, also with C_α–H bonds, react with $^1O_2$, giving product distributions that vary widely with structure and temperature in some cases. A temperature-dependent competition between an ene reaction (*C*-hydroperoxy adduct) and 1,2-cycloaddition to the C=N bond is proposed: Ito, Y.; Kyono, K.; Matsuura, T. *Tetrahedron Lett.* **1979**, 2253–2256.

(11) Nitronate anions are cleaved at the C=N bond to carbonyl products: Williams, J. R.; Unger, L. R.; Moore, R. H. *J. Org. Chem.* **1978**, *43*, 1271–1272. Our work (see text) confirms this result.

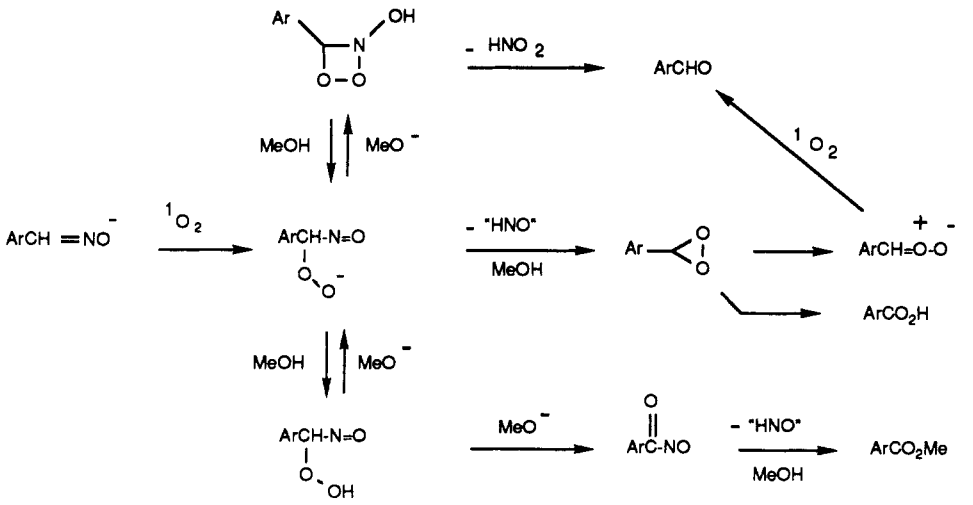
(12) Two cyclic nitrones have been investigated; one quenched $^1O_2$ while the other formed a *C*-hydroperoxy adduct by an ene reaction: Ching, T.-Y.; Foote, C. S. *Tetrahedron Lett.* **1975**, 3771–3774. The reactions of nitrones with $^1O_2$ are examined in the present work (see text).

(13) (a) Ene reaction: Gollnick, K.; Kuhn, H. J. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic: New York, 1979; p 287. See also: Foote, C. S. *Acc. Chem. Res.* **1968**, *1*, 104–110. (b) 1,2-Cycloaddition: Schaap, A. P.; Zaklika, K. A. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. N., Eds.; Academic: New York, 1979; p 173.

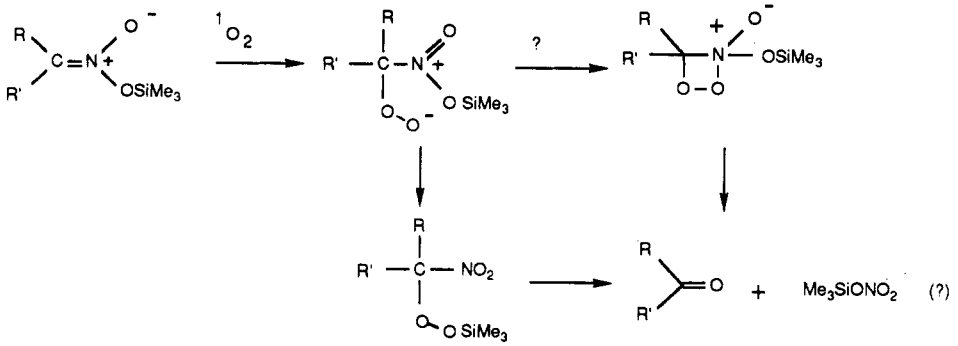
(14) (a) Gollnick, K.; Schenk, G. O. In *1,4-Cycloaddition Reactions*; Hamer, J., Ed.; Academic: New York, 1967; p 255. (b) Bloodworth, A. J.; Eggelte, H. J. In *Singlet Oxygen. Reaction Modes and Products*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. II, Part 1, p 93.

(15) (a) Gollnick, K.; Lindner, J. H. E. *Tetrahedron Lett.* **1973**, 1903–1906. (b) Davidson, R. S.; Tretheway, K. R. *J. Chem. Soc., Perkin Trans. 2*, **1977**, 173–178.

Scheme I. Photooxygenation of Aldoximate Anions



Scheme II. Photooxygenation of *O*-Silylnitronates



oxygen was demonstrated by controls in which reaction was attempted without the lamp, without the sensitizer, in some cases by using the singlet oxygen quencher, DABCO,[16] and in one case by substituting N_2 for O_2 as well.

In agreement with the results of others,[4] we find that whereas benzophenone oxime is cleaved by $^1O_2$ to benzophenone,[4a] other oximes are unreactive under our conditions. The oximes of cyclohexanone, cinnamaldehyde, *p*-tolualdehyde, *p*-nitrobenzaldehyde, *p*-(dimethylamino)benzaldehyde, and *p*-methylacetophenone are unchanged after 7–12 h of illumination at room temperature in CCl_4. Acetone oxime, a minor product in the reaction of *N*-isopropyl nitrones with $^1O_2$, also appears to be unreactive. We also attempted the reaction of *p*-(dimethylamino)benzaldehyde oxime at −78 °C (acetone-d_6), again with no conversion. We wondered if an unstable adduct might have formed, reverting quantitatively to reactants. However, the failure of the *O*-trimethylsilyl ethers of *p*-tolualdehyde oxime and *p*-methylacetophenone oxime to react with $^1O_2$ indicates that such an adduct, if formed, is not productively trapped by a neighboring silyl group.

Oximate anions are more electron rich than oximes. When the oximes of *p*-tolualdehyde and *p*-methylacetophenone are photooxygenated in methanol in the presence of rose bengal and 2 equiv of sodium methoxide, the disappearance of oximate is virtually complete after 3 h. In the case of the ketoximate, workup gave *p*-methylacetophenone (and a small amount of starting material). The aldoximate gave methyl *p*-toluate, *p*-toluic acid, and *p*-tolualdehyde in the ratio 9:7:1. Controls showed that these products are stable under the reaction conditions, hence are not formed from one another. Scheme I, which begins with electrophilic addition to carbon, is a reasonable path for the aldoximate reaction. Lack of a benzylic C–H bond in the ketoximate leaves only a path toward the ketone via a 1,2-cycloadduct according to this scheme. Partitioning of the 1,2-cycloadduct toward the carbonyl product should, in any event, be more favorable for ketone formation than for aldehyde formation, the carbonyl group being more stable as a ketone than an aldehyde.

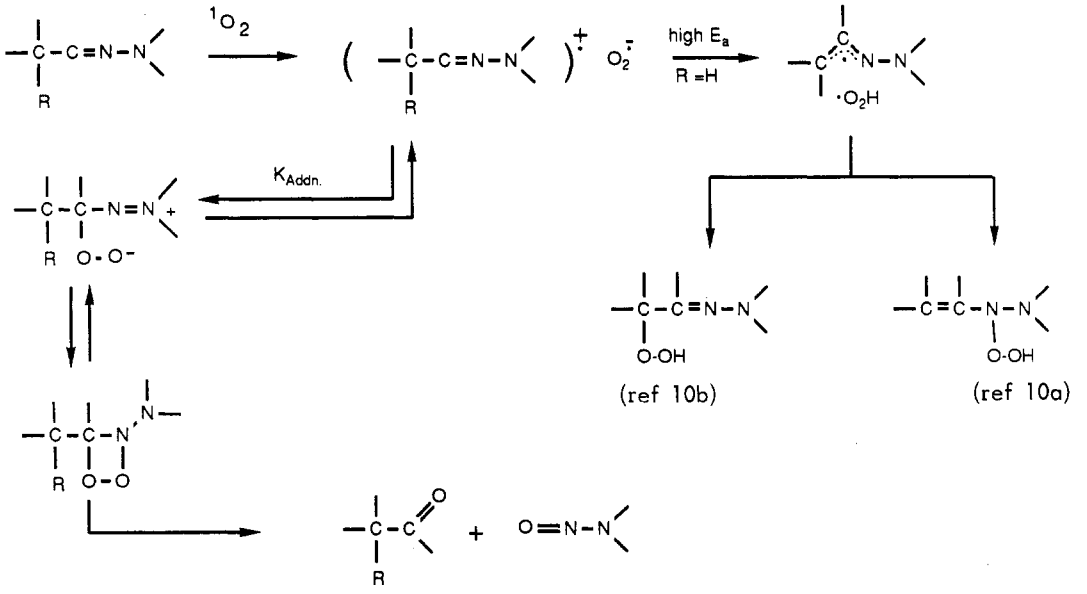
Nitronate anions are also electron rich; Williams et al.[11] have shown that these can be cleaved to carbonyl compounds, one of many ways to effect this transformation. We have investigated just one nitronate, that of 1-nitrohexane. Photooxygenation in D_2O/DMSO-d_6 (5:1, v/v) with 1 equiv of NaOD and a small amount of rose bengal gave no detectable hexanal after 2 h at room temperature. However, addition of CCl_4, TPP, and 0.5 equiv of cetyltrimethylammonium bromide gave complete conversion to hexanal after an additional 2 h of light. The same reaction can be carried out successfully by using methanol with rose bengal. Oxygen is less soluble in water and in DMSO by about a factor of 10 compared with ordinary organic solvents.[17] This fact can explain our failure to observe a reaction between the nitronate ion and $^1O_2$ in the D_2O/DMSO mixture.

O-Silylnitronates are easily prepared and offer promise as synthetic intermediates.[18] We have examined the

(16) Ouannes, C.; Wilson, T. *J. Am. Chem. Soc.* **1968**, *90*, 6527–6528.

(17) Battino, R. *Oxygen and Ozone. Solubility Data Series*; IUPAC Vol. 7; Pergamon Press: Oxford, 1981.

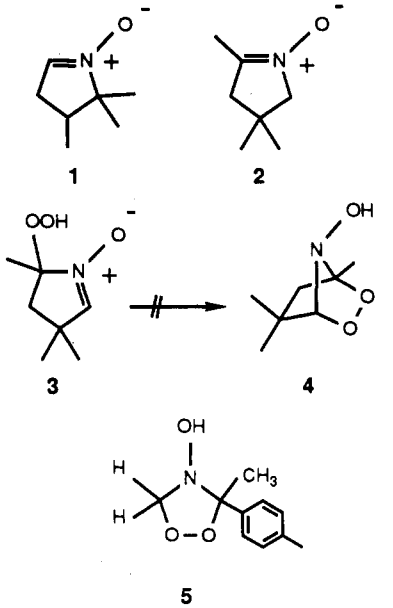
Scheme III. Photooxygenation of N,N-Disubstituted Hydrazones



room-temperature photooxygenation (CCl_4, TPP) of the *O*-trimethylsilyl derivatives of nitroethane, 2-nitropropane, 1-nitrohexane, nitrocyclohexane, phenylnitromethane, and *p*-tolylnitromethane. Reaction is rapid (2 h or less) and gives apparently quantitative yields of the corresponding aldehyde or ketone.[19] Scheme II rationalizes this facile conversion. Although the 1,2-cycloadduct is an obvious candidate, it is not a required intermediate. Intramolecular silyl transfer avoids four-membered-ring formation and is an attractive alternative.[20]

Hydrazones which have been tested by others are those with an N—H bond,[3c] or N,N-disubstituted hydrazones with a C—H bond α to the C=N carbon.[10] We have begun to examine hydrazones bearing neither N–H nor C_α–H bonds. At room temperature in CCl_4 or CH_2Cl_2, the *N*-methyl-*N*-phenylhydrazones of *p*-tolualdehyde and *p*-methylacetophenone are unchanged by 22 h of TPP-sensitized photooxygenation. However, when reaction is carried out at −78 °C, C=N cleavage occurs, giving the aldehyde or ketone plus *N*-nitroso-*N*-methylaniline. This result resembles that of Ito et al.[10b] except that their hydrazones, having a secondary or tertiary C_α–H bond, also have an ene-type reaction available to them. In fact, at room temperature, Ito's substrates prefer the ene pathway as opposed to C=N cleavage or (as in our cases) no reaction. These results seem to call for an exothermic stage prior to C=N cleavage. This stage would become progressively disfavored at higher temperatures compared with the rate of secondary or tertiary C_α–H cleavage, which then would become competitive, leading toward an *N*-hydroperoxy adduct[10a] or a *C*-hydroperoxy adduct.[10b] A scheme that encompasses these suggestions as well as those of Ito et al.[10b] and Friedrich et al.[10a] is given as Scheme III.

Nitrones have been scarcely examined by photooxygenation. Ching and Foote reported that compound 1 does not react in methylene blue sensitized photooxygenation (−63 °C, $CDCl_3$), but that it does quench $^1O_2$.[12] Compound 2 (same conditions) forms the *C*-hydroperoxy adduct 3 by an ene-type reaction; 3 decomposes violently upon warming.



We imagined that the formally negative oxygen of a nitrone would activate the C=N carbon toward electrophilic reagents and have examined the reactions of a series of *C*-aryl aldonitrones and ketonitrones with $^1O_2$. Dye-sensitized photooxygenation of *N*-methylnitrones (−78 to 25 °C, CCl_4, $CDCl_3$, CH_2Cl_2, acetone-d_6) produced the general results shown in eq 1.

$$\mathrm{ArC(R){=}\overset{+}{N}(CH_3)\overset{-}{O} + {}^1O_2 \rightarrow ArCOR + ArC(R){=}NOH + HCO_2H + HCONHOH} \quad (1)$$

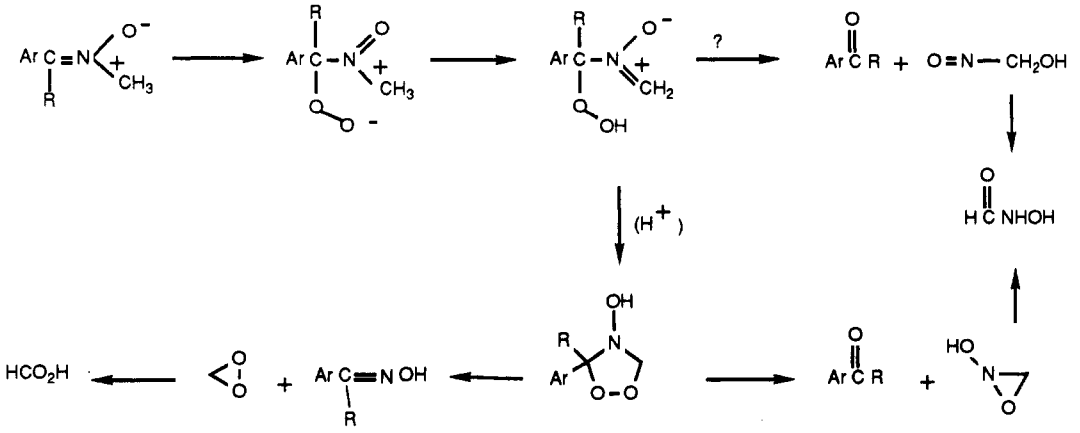
In some cases very small amounts of other, unidentified compounds were also produced. Products and product ratios are tabulated in Table II. These mixtures are more

(18) (a) Kashutina, M. V.; Ioffe, S. L.; Tartakovskii, V. A. *Dokl. Akad. Nauk SSSR* **1974**, *218*, 109–112. (b) Torssell, K.; Zeuthen, O. *Acta Chem. Scand. B* **1978**, *32*, 118–124. Andersen, S. H.; Das, N. B.; Jorgensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. *Acta Chem. Scand. B* **1982**, *36*, 1–14. (c) Colvin, E. W.; Seebach, D. *J. Chem. Soc., Chem. Commun.* **1978**, 689–690. Colvin, E. W.; Beck, A. R.; Bastani, B.; Seebach, D.; Kai, Y.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63*, 697–710. (d) Olah, G. A.; Gupta, B. G. B.; Narang, S. C.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 4272–4275. Olah, G. A.; Gupta, B. G. B. *Synthesis* **1980**, 44–45.

(19) Adventitious moisture causes formation of the original nitroalkane to accompany C=N cleavage.

(20) Intramolecular silyl transfer between oxygens is rapid in *O*-silylnitronates themselves (ref 18c, 1980).

Scheme IV. Photooxygenation of *N*-Methylnitrones[a]



[a] R = H, CH_3.

complex than those encountered in our studies with other C=N compounds; in fact, the product ratios can be changed somewhat by addition of solid $NaHCO_3$ to the reactions. Despite this complexity, several observations allow further discussion. (1) *N*-Methylnitrones undergo reaction at the *N*-methyl group whether or not a *C*-methyl group is present. (2) *N*-Isopropylnitrones show similar product mixtures, but also give acetone and a trace of acetone oxime (entry 4, Table II). (3) Nitrones that have no CH unit attached to nitrogen (entries 9–11, Table II) react very slowly or not at all. (4) *C*-Styryl-*N*-methylnitrone reacts with $^1O_2$ in $CCl_4/CDCl_3$ (3:1, v/v) and in acetone-d_6 solution, but not in methanol-d_4. Hydrogen bonding to the nitrone oxygen would reduce reactivity toward electrophilic $^1O_2$. (5) The ratio of products, oxime/formic acid, formed from *N*-methylnitrones is near unity; where oximes were not observed (entries 3 and 6, Table II), neither was formic acid. We believe that these two products are coupled. (6) Formohydroxamic acid (largely insoluble in chlorinated hydrocarbon solvents) was detected as a product of the *N*-methylnitrone reactions. We infer that this product and the aldehyde or ketone product in the mixture are coupled, but we do not have quantitative evidence on this question. (7) In one experiment, the photooxygenation of *C,N*-dimethyl-*C*-*p*-tolylnitrone at 0 °C in $CCl_4/CDCl_3$ (3:1, v/v), we detected an intermediate having ^1H NMR resonances at δ 4.91 and 4.48 (both doublets, J = 6.3 Hz) and at δ 1.76 (singlet). The peak area ratio of these resonances was 1:1:3, respectively. Also present in the spectrum were the peaks of the products given in Table II, entry 5. Upon warming to room temperature, the three resonances described above disappeared. We believe that these observations signify the formation and decomposition of compound **5**, a 4-hydroxy-1,2-dioxa-4-azacyclopentane. We assign the singlet at δ 1.76 to the methyl group on the five-membered ring. The doublets at δ 4.91 and 4.48 are assigned to the two protons on that ring on the basis of the following calculation. The protons at C-3 and C-5 of *cis*-3,5-diphenyl-1,2-dioxa-4-azacyclopentane have δ 5.94.[21] For comparison with structure **5**, we apply upfield corrections of 1.30 ppm for the attached phenyl group and 0.25 ppm for the methine environment.[22] A final downfield correction of ca. 0.3 ppm is necessary for the presence of the N–OH group in **5**.[23] This brings the calculated shift to δ 4.65, a value close to and between our observed shifts. The higher field resonances we assign to the proton trans to the *p*-tolyl group in **5** while the doublet at δ 4.91 is due to the cis proton.[21] We speculate that, in the experiment of Ching and Foote,[12] the analogous ring closure of compound **3** to **4** does not occur owing to the increased strain in **4**. The thermal decomposition of **3** could, of course, pass through **4**.

A pathway that rationalizes the reactions of singlet oxygen with *C*-aryl-*N*-methylnitrones is shown in Scheme IV.[24] In the last stage of the scheme, the 4-hydroxy-1,2-dioxa-4-azacyclopentane, a mononitrogen analogue of an ozonide, partitions to the observed products. For *C*-styryl-*N*-methylnitrone (entry 7, Table II), an additional path via electrophilic conjugate addition of $^1O_2$ to the benzylic carbon could lead to the small amount of benzaldehyde observed, while autoxidation of cinnamaldehyde explains the trace of cinnamic acid in that product mixture. We see the reactions of the *N*-isopropylnitrones as qualitatively similar; routes giving acetone should also produce N_2O, but this expectation has not been probed.

The ene pathway is unavailable to *N*-phenyl- and *N*-*tert*-butylnitrones; however, some oxidative cleavage could be observed (entries 9 and 10, Table II). A relatively inefficient 1,2-cycloaddition of $^1O_2$ to the C=N bond would, after ring cleavage, account for the products. Thus, there are at least two mechanisms by which nitrones react with singlet oxygen.

Summary. The reactivity patterns of C=N compounds toward singlet oxygen indicate that reaction is facilitated by electron donors attached to nitrogen. We suggest that this feature aids combination of electrophilic $^1O_2$ with the C=N carbon. Subsequent transformations depend on the details of substrate structure. In the case of nitrones having CH attached to the C=N nitrogen, an ene-type reaction occurs, and this event may be followed by cyclization to a 4-hydroxy-1,2-dioxa-4-azacyclopentane intermediate. Product formation, whether by homolytic or heterolytic fragmentation, ensues from the intermediates described herein and shown in the schemes. Nitrones

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(24) Initial electron transfer, as in Scheme III, or the fleeting existence of a 1,3-cycloadduct are not ruled in or out by our observations. An argument against formation of a 1,3-cycloadduct is that ozonolysis of imines, a reaction that could go through the same 1,3-cycloadduct, does not give the same products as singlet oxygenation of nitrones. Moreover, were ozonolysis of imines to produce oximes, these would be further transformed with the net consumption of more ozone than is observed. See: Bailey, P. S. *Ozonation in Organic Chemistry*; Academic: New York, 1982; Vol. II, pp 225–235.

unable to react by an ene mechanism can nevertheless be slowly cleaved to carbonyl compounds by $^1O_2$. The carbonyl-forming C=N cleavages of nitronate anions, *O*-silylnitronates, ketoximate anions, and the *N*-methyl-*N*-phenylhydrazones of aromatic aldehydes and ketones are clean; these reactions are of potential synthetic use. Aldoximate anions and nitrones can, however, give mixtures of products.

Experimental Section

^{1}H NMR spectra were obtained with a Varian EM-360 spectrometer and with a GE-Nicolet QE 300 spectrometer. The latter instrument was also used for the 75-MHz ^{13}C spectra. IR spectra were obtained with a Nicolet 20DBX FT-IR instrument. Except as described below, the compounds used were commercial products. Nondeuterated solvents were dried and distilled before use. Melting points are uncorrected.

Oximes. These compounds were made by a standard procedure.[25] Their melting points were in agreement with literature values.

***O*-Silyloximes.** The *O*-trimethylsilyl derivatives of the oximes of *p*-tolualdehyde and *p*-methylacetophenone were made by combining equimolar amounts of the oxime, trimethylsilyl chloride, and triethylamine in dried diethyl ether. The resulting white precipitate was filtered through Celite and washed with dry ether under a blanket of N_2. Removal of solvent left a residual oil, which was dissolved in dry CCl_4. The 60-MHz ^{1}H NMR spectra of these solutions showed the silylated oximes to be pure, uncontaminated by the parent oxime: ^{1}H NMR for the silylaldoxime (CCl_4) δ 0.23 (9 H, s), 2.36 (3 H, s), 7.08 (2 H, d, J = 8 Hz), 7.43 (2 H, d, J = 8 Hz), 8.06 (1 H, s); for the silylketoxime (CCl_4) δ 0.24 (9 H, s), 2.21 (3 H, s), 2.37 (3 H, s), 7.13 (2 H, d, J = 8 Hz), 7.56 (2 H, d, J = 8 Hz).

Arylnitromethanes. Phenylnitromethane and (*p*-methylphenyl)nitromethane were synthesized by the method of Avery and Butler.[26]

***O*-Silylnitronates.** The *O*-trimethylsilyl derivatives of nitroalkanes were made by the procedure of Torssell[18b] or that of Colvin and Seebach.[18c]

Di-*p*-tolylfuroxane. This compound was made according to Mukaiyama and Hoshino.[27] It was recrystallized from 95% ethanol, giving pale yellow needles: mp 142–142.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.388 (3 H, s), 2.409 (3 H, s), 7.197 and 7.170 (2 H, d, J = 8.1 Hz), 7.204 and 7.177 (2 H, d, J = 8.1 Hz), 7.380 and 7.353 (2 H, d, J = 8.1 Hz), 7.387 and 7.360 (2 H, d, J = 8.1 Hz).

***N*-Methyl-*N*-phenylhydrazones.** These hydrazone derivatives of *p*-tolualdehyde and *p*-methylacetophenone were prepared by the method of Yao and Resnick.[28] The aldehyde derivative melts at 118.5–119 °C (CH_3OH/H_2O): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (3 H, s), 3.27 (3 H, s), 6.88 (1 H, tt, J = 6.9, 1.5 Hz), 7.129 (2 H, d, J = 8.1 Hz), 7.25–7.34 (4 H, complex), 7.39 (1 H, s), 7.554 (2 H, d, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.38, 32.95, 115.28, 120.45, 126.17, 129.05, 129.36, 132.22, 134.26, 137.62, 148.14. The ketone derivative melts at 52.5–53 °C (CH_3OH/H_2O): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (3 H, s), 2.37 (3 H, s), 3.13 (3 H, s), 6.88 (1 H, t, J = 7.2 Hz), 6.947 (2 H, d, J = 8.1 Hz), 7.20–7.29 (4 H, complex), 7.810 (2 H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 16.32, 21.30, 42.63, 115.43, 119.87, 126.63, 128.80, 129.07, 135.51, 139.96, 148.54, 151.39.

***C*-*p*-Tolyl-*N*-methylnitrone.** This aldonitrone was prepared by the reaction of *p*-tolualdehyde with *N*-methylhydroxylamine:[25] mp 116.5–118.5 °C (lit.[29] mp 122–124.5 °C); ^{1}H NMR ($CDCl_3$) δ 2.37 (3 H, s), 3.87 (3 H, s), 7.22 (2 H, d, J = 8.0 Hz), 7.30 (1 H, s), 8.14 (2 H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 21.48, 53.79, 127.98, 128.12, 128.77, 133.50, 139.64.

***C*-(*p*-Nitrophenyl)-*N*-methylnitrone.** Prepared as above,[25] this nitrone melted at 210–211.5 °C: small yellow needles from ethanol/acetone (lit.[30] mp 208 °C); ^{1}H NMR ($CDCl_3$) δ 3.96 (3 H, s), 7.53 (1 H, s), 8.265 (2 H, d, J = 8.9 Hz), 8.384 (2 H, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 55.15, 123.82, 128.65, 133.11, 136.00, 147.83.

***C*-[*p*-(Dimethylamino)phenyl]-*N*-methylnitrone.** Prepared as above,[25] this nitrone melted at 131.5–134 °C: ^{1}H NMR ($CDCl_3$) δ 2.887 (6 H, s), 3.663 (3 H, s), 6.561 (2 H, d, J = 9.0 Hz), 7.098 (1 H, s), 8.033 (2 H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 39.57, 52.92, 110.73, 118.16, 130.01, 135.42, 151.07.

***C*-*p*-Tolyl-*N*-isopropylnitrone.** Prepared as above,[25] the compound melts at 47.5–48.5 °C (95% ethanol): ^{1}H NMR ($CCl_4/CDCl_3$, 4:1) δ 1.478 (6 H, d, J = 6.6 Hz), 2.378 (3 H, s), 4.144 (1 H, sept, J = 6.6 Hz), 7.162 (2 H, d, J = 7.8 Hz), 7.324 (1 H, s), 8.071 (2 H, d, J = 7.8 Hz); ^{13}C NMR ($CCl_4/CDCl_3$, 4:1) δ 21.04, 21.78, 67.47, 128.40, 128.51, 129.06, 130.97, 139.78.

***C*-Styryl-*N*-methylnitrone.** Prepared as above,[25] this nitrone melted at 82–84 °C (CH_2Cl_2; lit.[30] mp 87 °C): ^{13}C NMR ($CDCl_3$) δ 52.40, 118.51, 127.31, 128.86, 129.18, 136.13, 137.38, 137.94.

***C*-*p*-Tolyl-*N*-phenylnitrone.** Prepared by the method of Wheeler and Gore,[31] the compound melted at 90.5–91 °C (lit.[36] mp 92.5–93 °C): ^{1}H NMR ($CDCl_3$) δ 2.42 (3 H, s), 7.28 (2 H, d, J = 7.5 Hz), 7.44–7.51 (3 H, complex), 7.78 (2 H, d, J = 7.5 Hz), 7.88 (1 H, s), 8.29 (2 H, d, J = 7.5 Hz). The spectrum is in good agreement with that reported by Koyano and Suzuki.[37]

***C*,*N*-Dimethyl-*C*-*p*-tolylnitrone.** This ketonitrone was prepared by Exner's method.[32] It is semisolid at room temperature. Its ^{1}H NMR spectrum ($CDCl_3$) is in excellent agreement with that reported by Yoshimura et al.[33] We find the following: δ 2.390 (3 H, s), 2.425 (3 H, s), 3.657 (3 H, s), 7.154 (2 H, d, J = 8.1 Hz), 7.243 (2 H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 20.30, 21.25, 48.73, 127.47, 129.55, 133.45, 139.29, 147.68.

***C*,*N*-Dimethyl-*C*-(*p*-nitrophenyl)nitrone.** Prepared by Exner's method,[32] the compound was purified by TLC on silica gel (CH_3OH/EtOAc, 1:3): yellow solid, mp 154–156 °C; ^{1}H NMR ($CDCl_3$) δ 2.471 (3 H, s), 3.710 (3 H, s), 7.506 (2 H, d, J = 8.7 Hz), 8.330 (2 H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 20.10, 49.29, 124.17, 128.88, 142.14, 145.27, 147.82. Bjørgo et al.[34] give mp 147–148 °C and ^{1}H NMR data almost identical with ours.

Photooxygenation Procedure. In a typical experiment, 150–200 mg of substrate was dissolved in 4 mL of solvent in a small flask with a stir bar. Enough sensitizer to make a concentration of ca. 10^{-4} M was added. The flask was flushed with oxygen and then connected either to a gas buret containing excess O_2 at a slight positive pressure or to a thick-walled balloon inflated with O_2. Temperature was controlled with running water, an ice bath, or a dry-ice bath. Stirring was begun and a 250-W sodium vapor lamp turned on. Periodically samples were withdrawn for examination by NMR or IR spectroscopy or by TLC. Upon disappearance of the substrate, the reaction solution was washed with water and the organic layer dried over anhydrous Na_2SO_4. Removal of solvent left a residue, which was analyzed by NMR, IR, and, in some cases, TLC. When basic methanol was the solvent, the workup included addition of water, adjustment of pH to ca. 2, and extraction with CCl_4 prior to drying and solvent removal. When acetone was used, we simply evaporated the solvent and dissolved the residue in an appropriate solvent for further examination.

Product Identification. Organic products were identified by comparison of ^{1}H and ^{13}C NMR spectra with those of authentic samples, as well as by TLC comparison. In some runs the products were isolated by preparative TLC. Formic acid was identified

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by its characteristic CH resonance at δ 8.04; upon extraction with water, this feature disappeared. The reactions of *N*-methylnitrones in halogenated hydrocarbon solvents produced an insoluble material, soluble in water, which gave a strong $FeCl_3$ test: ^1H NMR (D_2O, DSS internal standard) δ 8.20 (s), 4.60 (HDO); IR (KBr, cm^{-1}) ca. 3500–2700 (br), 1668, 1648, 1385, 1351, 1190. An authentic sample of formohydroxamic acid was prepared by Schroeter's method,[35] mp 72–74 °C (lit.[35] mp 72–74 °C). Its ^1H NMR and IR spectra were identical in all respects with those of the reaction product.

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Synthesis of Two Useful, Enantiomerically Pure Derivatives of (*S*)-4-Hydroxy-2-cyclohexenone

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In connection with several research objectives in our laboratory, we perceived a need for protected versions of the *S* enantiomer of 4-hydroxycyclohexenone (**5**). Since the envisioned compounds were to serve as enantiomerically pure educts in extended journeys, the prospect of resolution was discouraging. Below is described a synthetic route by which substantial quantities of optically pure compounds (see **6** and **7**) can be prepared without recourse to resolution.

The synthesis started with compound **1**, which had been obtained in two easy steps from D(−)-quinic acid by Trost and co-workers.[1] Oxidative cleavage of the vicinal diol ($NaIO_4$) afforded ketone **2**. Elimination of the secondary alcohol via reaction with methanesulfonyl chloride–triethylamine produced enone **3**. Hydrogenation of **3** was carried out with Pearlman's catalyst[2] at 50 psi to give ketone **4** in 75% yield. Fortunately, it was not necessary to obtain **5**[3] in order to reach the goal system **6**. Thus, treatment of **4** with *tert*-butyldimethylsilyl chloride and DBU afforded **6** in 87% yield.

We were unable to devise a corresponding one-step conversion to go from **4** to the *p*-methoxybenzyl protected derivative **7**. To reach that compound it was necessary for us to pass through **5**. This compound was obtained by base (DBU or K_2CO_3) induced elimination of **4** in 49% yield. Compound **5** is quite unstable and was transformed to **7** (ca. 60%) through the use of *p*-methoxybenzyltrichloroacetimidate in the presence of boron trifluoride etherate.[4]

Compounds **6** and **7** are particularly versatile because they undergo reaction with a range of nucleophiles. As part of our synthetic route to FK-506,[5] it was found that compound **7** reacts with lithium dimethylcuprate to afford the *trans*-3,4-disubstituted product **8** (R = α-Me; R′ = PMB). By contrast, in connection with our recently completed total synthesis of ML-236A,[6] it was found that Lewis acid (HgI_2) induced addition of silylketene acetals to **6** affords cis product **9** (R = β-CH_2CO_2Et; R′ = TBS) (Scheme I).

We are currently studying the factors that are responsible for the remarkable preference for cis products in the Lewis acid catalyzed reaction. Other applications of these compounds will be described.

Experimental Section

3,4-*O*-Isopropylidene-3(*R*),4(*S*),5(*R*)-trihydroxycyclohexanone (2). Triol **1**[1] (73 g, 0.34 mol) was dissolved in 900 mL of phosphate buffer pH 7, and the solution was cooled to 0 °C. Sodium periodate (94 g, 0.44 mol) was added in portions. After the addition, the ice bath was removed and the mixture was stirred at room temperature for 1 h. The aqueous mixture was then extracted with methylene chloride (8 × 200 mL). The extracts were filtered through a mixture of magnesium sulfate and Celite. The solvent was evaporated to afford 53.6 g (86%) of a white solid. A small amount of the compound was purified by flash chromatography (ethyl acetate–hexanes, 1:1) or recrystallization (Et_2O) for characterization: mp (Et_2O) 80–81 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 4.71 (m, 1 H, 3-H), 4.31 (dt, 1 H, J = 7.1, 2.5 Hz, 4-H), 4.22 (dd, 1 H, J = 6.2, 2.5 Hz, 5-H), 2.82 (dd, 1 H, J = 17.6, 3.6 Hz, 2-H), 2.66 (dm, 2 H, J = ~17.6 Hz, 2,6-H), 2.59 (b s, 1 H, 3-OH), 2.44 (dm, 1 H, J = ~17.9 Hz, 6-H), 1.44 and 1.36 (2 s, 2 × 3 H); IR ($CDCl_3$) 3580, 3420, 2970, 2890, 1710, 1375, 1250, 1205, 1135, 1060, 1050 cm^{-1}; EIMS m/z (relative intensity) 186 (1), 171 (100), 129 (61), 111 (55); $[\alpha]_D$ +141.24° (*c* 0.89, $CHCl_3$). Anal. Calcd for $C_9H_{14}O_4$: C, 58.04; H, 7.58. Found: C, 58.20; H, 7.48.

4,5-*O*-Isopropylidene-4(*S*),5(*R*)-dihydroxy-2-cyclohexen-1-one (3). To a solution of **2** (53.6 g, 0.30 mol) and triethylamine (125 mL, 0.90 mol) in 900 mL of CH_2Cl_2 cooled to 0 °C was added over a period of 40 min a solution of methanesulfonyl chloride (28 mL, 0.36 mol) in 90 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature for 2 h after addition was complete. Then, the reaction was washed with water (3 × 200 mL), and the aqueous layers were extracted with ether (2 × 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated. Trituration of the brown oil with ether followed by filtration through a short pad of silica gel (eluted with ether) gave, after solvent removal, desired compound **3** (42 g, 83%). A small amount of **3** was purified by flash chromatography (ethyl acetate–hexanes, 1:3) or Kugelrohr distillation (1 mmHg) for characterization. Distillation gave a white solid: mp 39–40 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 6.63 (dd, 1 H, J = 10.4, 2.3 Hz, 3-H), 6.02 (d, 1 H, J = 10.4 Hz, 2-H), 4.69 (m, 2 H, 4,5-H), 2.91 (dd, 1 H, J = 17.6, 2.5 Hz, 6-H), 2.68 (dd, 1 H, J = 17.6, 3.6 Hz, 6-H), 1.38 (s, 3 H), 1.37 (s, 3 H); IR ($CDCl_3$) 2980, 2910, 1680, 1385, 1370, 1255, 1230, 1155, 1140, 1060 cm^{-1}; EIMS m/z (relative intensity) 168 (0.5), 153 (100), 111 (84); $[\alpha]_D$ +147.50° (*c* 0.48, $CHCl_3$). Anal. Calcd for $C_9H_{12}O_3$: C, 64.26; H, 7.20. Found: C, 64.31; H, 7.38.

3,4-*O*-Isopropylidene-3(*R*),4(*S*)-dihydroxycyclohexanone (4). Cyclohexenone **3** (41 g, 0.24 mol) was hydrogenated in several portions using a Parr shaker (50 psi). The compound (~8 g) was dissolved in 100 mL of EtOAc, and 300 mg of the Pearlman's catalyst was added. The reaction was complete after 24 h. The mixture was filtered through Celite, washed with EtOAc (200 mL), and concentrated. The combined crude was distilled under vacuum (85 °C, 1.5 mmHg) to give 31.1 g (75%) of desired compound **4** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 4.65 (m, 1 H, 3-H), 4.54 (dt, 1 H, J = 7.5, 2.7 Hz, 4-H), 2.66 (dd, 1 H, J = 16.9, 2.7 Hz, 2-H), 2.50 (dd, 1 H, J = 18.5, 4.9 Hz, 6-H), 2.43 (dd, 1 H, J = 16.9, 3.7 Hz, 2-H), 2.23 (dt, 1 H, J = 18.5, 3.2 Hz, 6-H), 2.08 (dm, J = 14.8 Hz, 5-H), 1.86 (~tdd, J = 14.8, 4.3, 3.2 Hz, 5-H), 1.42 (s, 3 H), 1.34 (s, 3 H); IR ($CHCl_3$) 3020, 2930, 1720,

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