On the Facile Regeneration of Carbonyl Compounds by Oxidative Cleavage of Hydrazones Using Dioxiranes

Anna Altamura,† Ruggero Curci,* and John O. Edwards‡

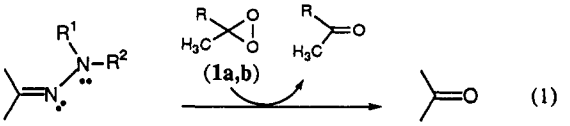
Centro CNR. "M.I.S.O.", Dipartimento di Chimica, Università di Bari, via Amendola 173, I-70126 Bari, Italy

Received August 2, 1993

The formation of hydrazone derivatives is a common method for the isolation and purification of carbonyl compounds; purification of these derivatives followed by regeneration of the parent ketone is a good procedure for isolation of the desired ketone from a complex mixture.[1] A number of procedures are available for the regeneration of carbonyls from hydrazones. However, it is known that direct hydrolysis and/or exchange methods, as catalyzed by strong acids, can lead to condensation byproducts or hydrolysis of sensitive protecting groups.[1,2] In these cases, viable alternatives may consist of methods of oxidative cleavage in organic solvents, or oxidative hydrolysis using a variety of reagents,[1,2] including peroxides.[2b-d]

On the other hand, oxidations of organic substrates employing dioxiranes (a new class of powerful oxidants), either *in situ*[3] or separated in solution, of their parent ketone[4] often carry the advantages of high selectivity, mild reaction conditions, and ease of product isolation. Most commonly, dioxiranes employed are of the type $R(CH_3)CO_2$ (1). Thus, dimethyldioxirane (**1a**: R = CH_3)[4a-c] and the more reactive methyl(trifluoromethyl)dioxirane (**1b**: R = CF_3)[4d,e] have been applied to perform a variety of synthetic transformations,[5] including regeneration of the carbonyl moiety from acetals, ketals, and orthoesters,[6] as well as from Fischer-carbene complexes.[7]

Along these lines, quite recently it has been shown[8] that tosylhydrazones can be cleaved to the corresponding carbonyl compounds using dimethyldioxirane generated *in situ* from the reaction of acetone with potassium peroxymonosulfate. This prompts us to report on our own results concerning the use of dioxirane solutions in the oxidative cleavage of ketone hydrazones (eq 1).



(1)

R^1 = H, R^2 = Ar;
R^1 = H, R^2 = Ts
R^1 = R^2 = CH_3;
R^1, R^2 = - $\overset{*}{C}H(CH_2OCH_3)$-$CH_2CH_2CH_2$ - = *(SAMP)*

Examples shown in Table I demonstrate that dioxiranes are excellent reagents for the conversion of aryl- and dialkyl hydrazones, as well as of tosylhydrazones (which are more prone to hydrolytic cleavage), into carbonyl compounds.

The oxidations simply entailed addition of aliquots of standardized[4] dioxirane solution to the hydrazone substrates at the conditions given in Table I; solutions of 0.08–0.12 M dimethyldioxirane (**1a**) in acetone or of 0.8–1.2 M methyl(trifluoromethyl)dioxirane (**1b**) in 1,1,1-trifluoropropane (its ketone precursor, hereafter TFP[4d,e]) were obtained by following reported procedures.[4]

Inspection of data reported in Table I (entries 1–7) suggests that electron-withdrawing NO_2 groups on the phenyl substituent either at the $Ph(CH_3)C{=}N$ moiety of acetophenone phenylhydrazone or at the nitrogen end of cyclohexanone phenylhydrazone have a rate-retarding effect. Competitive kinetics experiments (see Experimental Section) showed that the oxidative cleavage of *m*-nitroacetophenone phenylhydrazone (**2b**) by dimethyldioxirane (**1a**) is ca. 1.7 times slower than that of acetophenone phenylhydrazone (**2a**); this demonstrates that the dioxirane acts as an electrophilic oxidant toward the substrates at hand. This conclusion is reinforced by the observation that the oxidation of more electron-rich hydrazones such as cyclohexanone *N,N*-dimethylhydrazone (**8**) and the SAMP-hydrazone (**9**)[9] by **1a** require a considerably shorter reaction time (entries 10 and 11). For substrates more reluctant to undergo oxidative cleavage by **1a**, i.e. those bearing electron-withdrawing NO_2 groups, employing the more reactive dioxirane **1b** results in faster rates and higher conversions (cf., entries 4–7).

As for the potential applications in synthesis, the transformations illustrated by entries 8 and 9 of Table I are particularly telling. In fact, for steroidal ketones separation of their hydrazone derivatives is a useful isolation procedure; however, in the ensuing regeneration of the parent carbonyl, one often wishes to avoid hydrolysis of sensitive protecting groups, such as the acetoxy functionality. Indeed, using dioxiranes to unmask the carbonyl moiety from both steroidal hydrazones **4** and **6** leaves the ester functionality untouched. Chemoselectivity is further illustrated by the fact that carbonyl regeneration in **6** also leaves the carbon–carbon double bond intact. It should be noted that, in the cleavage of 17β-acetoxy testosterone tosylhydrazone (**6**) (Table I), an initial dioxirane/substrate ratio > 2 results in substantial formation of the epoxy ketone derived from **7**, i.e. 17β-acetoxy-4α,5-epoxyan-

* To whom correspondence should be addressed.
† In partial fulfillment of the requirements for the Ph.D. degree.
‡ Chemistry Department, Brown University, Providence, RI 02912.

(1) For instance, see: (a) Greene, T. W., Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991; pp 212–213. See also references quoted therein.

(2) (a) Bergbreiter, D. E.; Momongan, M. in *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 2, pp 523–526. (b) Ho, T.-L.; Olah, G. A. *Synthesis* **1976**, 611. (c) Enders, D.; Bhushan, V. *Z. Naturforsch., Teil B.* **1987**, *42*, 1595. (d) Narayana, C.; Reddy, N. K.; Kabalka, G. W. *Synth. Commun.* **1992**, *22*, 2587. See also refs quoted therein.

(3) (a) Edwards, J. O.; Pater, R. H.; Curci, R.; Di Furia, F. *Photochem. Photobiol.* **1979**, *30*, 63. (b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758. (c) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670. (d) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155.

(4) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, *52*, 699. (c) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800. (d) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890. (e) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749. (f) Murray, R. W.; Singh, M.; Jeyaraman, R. *J. Am. Chem. Soc.* **1992**, *114*, 1346.

(5) For a recent review, see: Adam, W.; Hadjiarapoglou, L. P.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; Wiley, New York, 1992; Chapter 4, pp 195–219. See also refs quoted therein.

(6) Curci, R.; D'Accolti, L.; Fiorentino, M.; Fusco, C.; Adam, W.; González-Nuñez, M. E.; Mello, R., *Tetrahedron Lett.* **1992**, *33*, 4225.

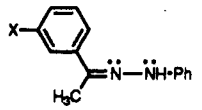
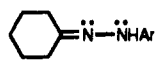
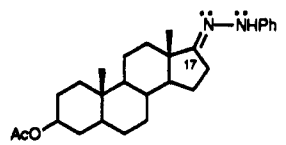
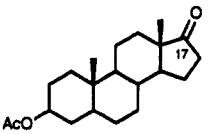
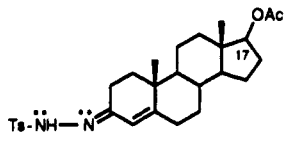
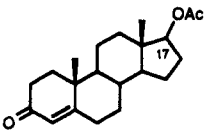
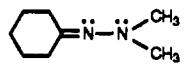
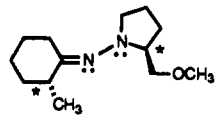
(7) Lluch, A. M.; Sanchez-Baeza, F.; Camps, F.; Messeguer, A. *Tetrahedron Lett.* **1991**, *32*, 5629.

(8) Jung, J. C.; Kim, K. S.; Kim, Y. H. *Synth. Commun.* **1992**, *22*, 1583.

(9) (a) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933. (b) Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. A. M. *Tetrahedron* **1984**, *40*, 1345. (c) Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 549.

0022-3263/93/1958-7289$04.00/0

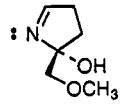
Table I. Oxidative Cleavage of Hydrazones into Ketones Using Dioxiranes[a]

entry	substrate	X	Ar	T (°C)	dioxirane[a]	reactn time	% conv[b]	product	% yield[c]
	 2a, b								
1		H		20	1a	30 min	>96	acetophenone	92
2		NO_2		20	1a	2 h	94	*m*-nitroacetophenone	87
	 3a–c								
3			C_6H_5	20	1a	30 min	>98	cyclohexanone	94[d]
4			$4\text{-}NO_2C_6H_4$	20	1a	3 h	96	cyclohexanone	95[e]
5			$4\text{-}NO_2C_6H_4$	0	1b	30 min	97	cyclohexanone	95
6			$2,4\text{-}(NO_2)_2C_6H_3$	20	1a	6 h	97	cyclohexanone	95
7			$2,4\text{-}(NO_2)_2C_6H_3$	0	1b	90 min	>98	cyclohexanone	95[f]
8	 4			20	1a	15 min	96	 5	98[f]
9	 6			20	1a[g]	1 h	99	 7	95[h]
10	 8			20	1a	3 min	>96	cyclohexanone cyclohexanone oxime	89 10[f]
11	 9[i]			0	1a[g]	5 min	>96	 10[j]	85[k]

[a] Unless noted otherwise, reactions were routinely run with initial dioxirane to substrate molar ratio ca. 3:1 in acetone for oxidations with **1a**; initial dioxirane to substrate molar ratio was ca. 2:1 in mixed solvent CH_2Cl_2/TFP (ca. 9:1) for oxidations with **1b**. [b] As determined (±2%) by GC. [c] Unless noted otherwise, data refer to yields (±2%) in product isolated after column chromatography and are based on the amount of substrate consumed; products were identified upon comparison of their ^1H NMR spectra and/or GC/MS data with those of authentic samples. [d] Nitrobenzene (ca. 15%) also detected by GC/MS of the reaction mixture. [e] Nitrobenzene (ca. 12%) and *p*-dinitrobenzene (ca. 9%) also detected by GC/MS. [f] Yield determined by GC and/or GC/MS; data compared with authentic cyclohexanone oxime (Aldrich). [g] Initial dioxirane to substrate molar ratio 2:1. [h] In the reaction mixture before separation, GC/MS and ^1H NMR showed small amounts (ca 1–2%) of 4α,5-epoxytestosterone acetate; running the reaction with initial dioxirane to substrate molar ratio 3:1 resulted in a mixture composed by ca. 30% testosterone acetate (**7**) and 70% of its 4α,5-epoxide (by GC/MS). [i] $[\alpha]^{20}_D = +218°$ (*c* 0.3, benzene); optical purity 94% (cf., ref 9a). [j] In the reaction mixture before separation, GC/MS and ^1H NMR showed that ketone **10** was accompanied by ca. 12% of the corresponding oxime. [k] $[\alpha]^{20}_D = -15.2°$ (neat), optical purity 92%; cf., $[\alpha]^{20}_D = -16.6°$ (neat), ref 9c.

drostan-3-one. Monitoring by GC/MS and ^1H NMR the reaction of dioxirane **1a** with **6** (**1a**/**6** ratio < 2:1) reveals no intermediate formation of epoxy ketone tosylhydrazone; therefore, oxidative cleavage of the NNHTs group in **6** is preceding epoxidation at the α,β-unsaturated C=C moiety.

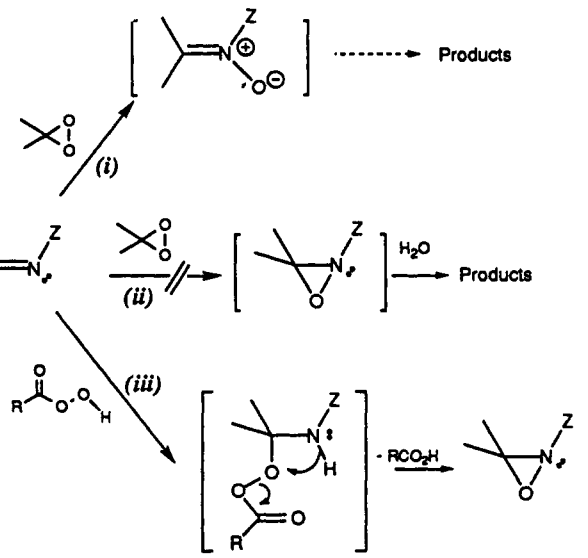
Also of interest is the high-yield oxidative cleavage of chiral hydrazone **9**; this yields rapidly optically active 2-methylcyclohexanone (**10**) with little loss (ca. 2%) of optical purity (Table I, entry 11, cf. footnotes *i* and *k*). The method shows promise to become a viable alternative to regeneration procedures devised by Enders and coworkers for SAMP/RAMP-hydrazones,[9] i.e. cleavage by ozone[9a,c] or oxidative cleavage by aqueous sodium perborate.[2c] In fact, the latter requires relatively long reaction times with yields commonly ranging 70–90%, while the former cannot be employed if there are other ozone-sensitive groups in the substrate hydrazone. In a preliminary attempt to determine the fate of the chiral auxiliary during the oxidation of SAMP-hydrazone **9** by dioxirane **1a**, GC/MS monitoring revealed the intermediacy of a cleavage product at *m*/*z* 129; this tentatively ascribed to intermediate **11**. Cyclic imine **11** could actually be isolated in optically active form from the reaction mixture (Experimental Section).



11

In other cases, the fate of the nitrogen-containing moiety of hydrazone substrates was only sporadically examined; the hint was that the primary oxidation intermediate is likely to suffer rapid further oxidation by the excess dioxirane necessary to bring the hydrazone cleavage to completion. For instance, nitrobenzene is the main

Scheme I



nitrogen-containing product derived from cyclohexanone phenylhydrazone (**3a**) (entry 3, Table I); however, in the cleavage of (*p*-nitrophenyl)hydrazone **3b**, besides the expected *p*-dinitrobenzene, nitrobenzene was also detected in the mixture of oxidation products (entry 4).

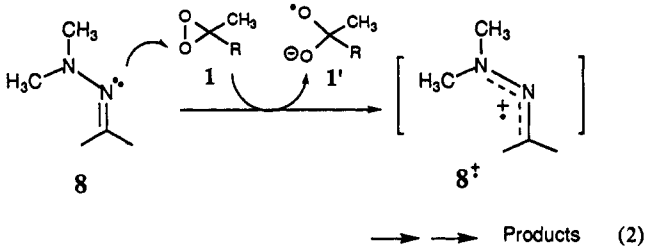
Concerning the reaction mechanism, it has been advanced[8] that the cleavage of hydrazones by dioxiranes proceeds through the formation of oxaziridine (Scheme I, path *ii*; with Z = NR'R''). This seems unlikely since formation of oxaziridines from imines (Z = R) normally requires *nucleophilic* oxidation via an addition–elimination mechanism[10] akin to that envisaged for the peracid conversion (path *iii*). By contrast, the aforementioned relative rate data indicate the dioxirane acts as an *electrophilic* oxidant toward hydrazones.

Furthermore, the dioxirane oxidation of imines has been shown to yield nitrones[10,11] (Scheme I, path *i*). Also, the cleavage of oximes (Z = OH) by dioxiranes[11] is thought to proceed via the corresponding *aci*-nitro compound by direct *N*-oxidation at the oxime nitrogen (path *i*).[11a] Therefore, it is likely that oxidative cleavage of hydrazones by dioxiranes initiates with direct electrophilic oxygen transfer to nitrogen. For aryl hydrazones, the cleavage might proceed through the sequence outlined in Scheme II.

In Scheme II, a side path (*i*) involving tautomerization of *N*-nitrosamine **12** to diazo hydroxide **13** was included in order to rationalize the observation that removal of the (*p*-nitrophenyl)hydrazone group in **3a** produces nitrobenzene, along with *p*-dinitrobenzene (entry 4, Table I).

Data in Table I suggest that, with respect to *N*-arylhydrazones, carbonyl regeneration is faster with *N,N*-dialkylhydrazones, such as cyclohexanone *N,N*-dimethylhydrazones (**8**) or the SAMP-hydrazone of 2-methylcyclohexanone (**9**). However, in both cases formation of the corresponding ketone oxime as byproduct is quite sizable (entry 10 and 11). This might be accommodated by envisaging the steps in Scheme III.

However, one should be aware that, akin to other electron-rich substrates[5,12] and to hydrazines,[13] one-electron as well as two-electron oxidation channels are available to dioxiranes. This was first substantiated during a study on dioxirane oxidation of polycyclic aromatic hydrocarbons.[12] In line with this, we find that when the *N,N*-dimethylhydrazone **8** is made to react with 1 equiv of **1a**, the reaction solution is not EPR silent. For instance, we find that a solution of 0.05 M **8** and 0.06 M **1a** in acetone at 20 °C yields a poorly resolved, non-symmetric EPR spectrum apparently consisting of seven broad lines (ΔH_{pp} > 5 G), separated on average by ca. 13 G. Such an EPR spectrum might be reconciled with radical cation $8^{\bullet+}$,[14] if one makes the assumption it has a planar or quasiplanar structure (eq 2) and that two weak external lines are submerged by background noise.



(2)

In fact, the EPR resonance of *planar* $8^{\bullet+}$ should consist of a nine-line spectrum, due to $a_{N(1)} < 1$[15] and to hyperfine splitting of N^2 to six H of the two methyl groups with $a_{N(2)}$ and a_H ranging from 10 to 13 G.[14,15] Under the conditions above, the said EPR absorption is seen to decay with time, fading away during 2–8 min. The transient radical intermediate is likely to be further oxidized to nonparamagnetic end products.

Concerning this, it is relevant that in the oxidation of **8** no products derived from transfer of methyl group of the dioxirane **1a** could be detected. In fact, Nelsen *et al.* recently reported[13] that certain sesquibicyclic hydrazines react with dimethyldioxirane (**1a**) mainly by CH_3 transfer, to yield the corresponding *N*-methylated hydrazinium cation. In that paper, as well as in a distinct article by Adam and co-workers,[16] the $CH_3^{\bullet}$ group being trapped was envisaged to arise from the O–O cleaved bis(oxy)-methylene radical anion $1^{\bullet-}$ (eq 2) by α-scission. This does not seem to fit with the chemistry so-far recorded[13,17] for such species. Indeed, as exemplified by $\mathbf{1b}^{\bullet-}$ (i.e., the radical anion generated from dioxirane **1b**), these radical anions react further with the parent dioxirane to yield the radical anion dimer $^-OCMe(R)OOCMe(R)O^{\bullet}$, rather than undergoing α-scission.[17] In these cases, it seems more reasonable that the $CH_3^{\bullet}$ trapped was formed by α-scission from dioxyl radicals $^{\bullet}OCMe(R)O^{\bullet}$.[18]

Obviously, the mechanisms of dioxirane cleavage of ketone aryl- and dialkylhydrazones have several interesting

(10) Boyd, D. R.; Coulter, P. B.; McGuckin, M. R.; Sharma, N. D.; Jennings, W. B.; Wilson, V. E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 301. See also references.

(11) (a) Crandall, J. K.; Reix, T. *J. Org. Chem.* **1992**, *57*, 6759. (b) Olah, G. A.; Liao, Q.; Lee, C.-S.; Prakash, G. K. S. *Synlett* **1993**, 427.

(12) Mello, R.; Ciminale, F.; Fiorentino, M.; Fusco, C.; Prencipe, T.; Curci, R. *Tetrahedron Lett.* **1990**, *31*, 6097.

(13) Nelsen, S. F.; Scamehorn, R. G.; De Filippis, J.; Wang, Y. *J. Org. Chem.* **1993**, *58*, 1657.

(14) Nelsen, S. F. In *Magnetic Properties of Free Radicals*; Fisher, H., Ed.; Landolt-Bornstein, "Numerical Data and Functional Relationships in Science and Technology"; Springer: Berlin, 1990; Vol. 17, Subvol. *h*, pp 154–156.

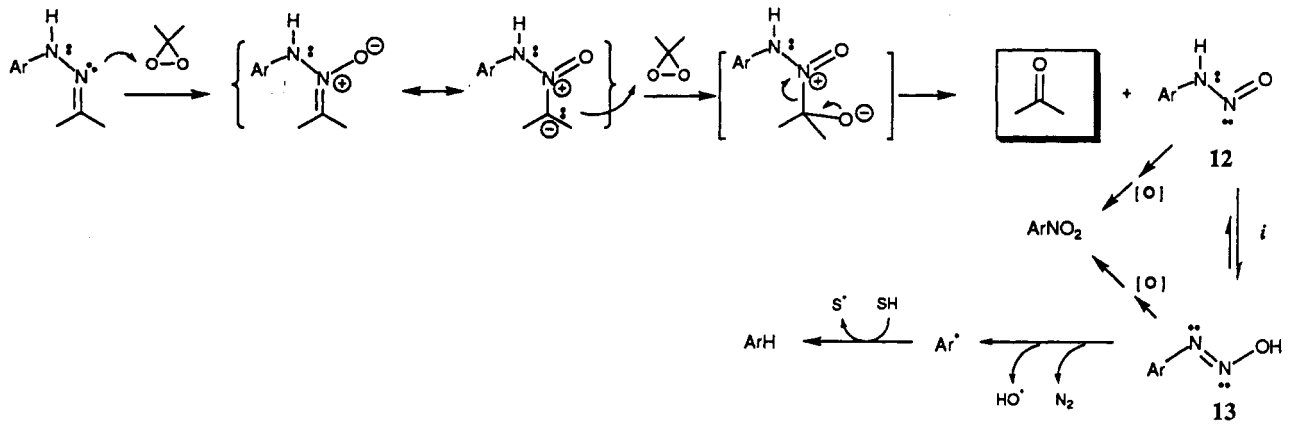
(15) Berndt, A.; Bolze, R.; Schnaut, R.; Woynar, H. *Angew. Chem.* **1981**, *93*, 400.

(16) Adam, W.; Bottle, S. E.; Mello, R. *J. Chem. Soc., Chem. Commun.* **1991**, 771.

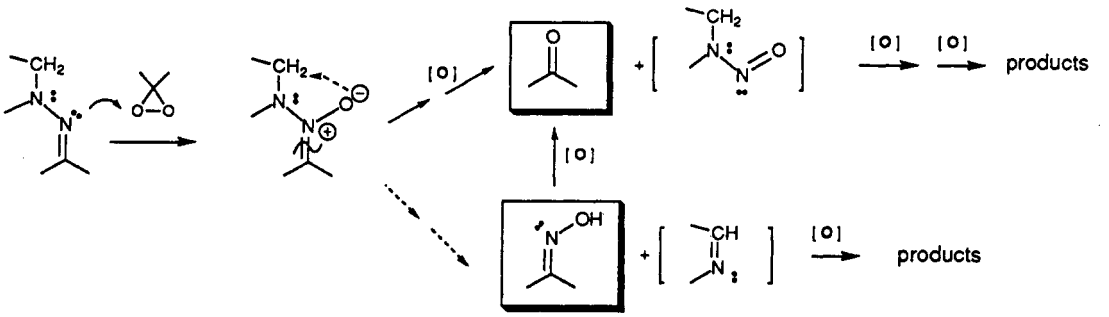
(17) Adam, W.; Asensio, G.; Curci, R.; Gonzalès-Nuñez, M. E.; Mello, R. *J. Am. Chem. Soc.* **1992**, *114*, 7654.

(18) Adam, W.; Curci, R.; Gonzalès-Nuñez, M. E.; Mello, R. *J. Am. Chem. Soc.* **1991**, *113*, 7654.

Scheme II



Scheme III



facets to pursue, raising a number of mechanistic incognita. For one, the fate of the oxidized hydrazone fragment needs to be investigated in more detail. Whatever the mechanistic features, the synthetic utility of applying dioxiranes to the transformation at hand seems undeniable. Indeed, in many synthetic sequences employing hydrazone derivatives (including azallyl metal reagents),[2] the final step is the selective removal of the hydrazone group. Results reported herein suggest that dioxiranes can be used to advantage in the selective, high-yield unmasking of carbonyls from their aryl-, tosyl-, or dialkylhydrazones, including SAMP- or RAMP-hydrazones. In view of the mild conditions and simplicity of isolation procedures, it is likely that dioxirane oxidation will quickly become a valuable addition to existing methods of regeneration of ketones from their hydrazones.[19]

Experimental Section

Equipment. Melting points and boiling points were not corrected. The ^1H and ^{13}C NMR spectra were recorded on a Varian Model XL 200 or Bruker AM 400 spectrometer; a Varian Model E 109 instrument was used to perform EPR experiments. Mass spectra were run employing a Hewlett-Packard Model 5970 mass-selective detector connected to a Model 5890 gas chromatograph; high resolution mass spectra were obtained on a Kratos MS80 RFA instrument (at Brown University). The FT-IR spectra were recorded on a Perkin-Elmer Model 1710 instrument, interfaced with a Model 7300 data station. Optical rotations were measured employing a Perkin-Elmer Model 241 MC spectropolarimeter. The GLC analyses were performed on a Perkin-Elmer Model 3800 chromatograph, equipped with a Epson Model FX 850 data station, on a SE 30, 30 m × 0.25 μm i.d. capillary column. A Fischer SPALTROHR microcolumn was used to perform fractional distillations. Other equipment and methods employed have been described previously.[4e]

Materials. All solvents, starting materials, and compounds used as reference in product analyses were of the highest purity commercially available; further purification, whenever appropriate, was achieved by following standard methods. Purified methylene chloride, acetone, and 1,1,1-trifluoro-2-propanone (TFP) (bp 22 °C) solvents were stored over 5-Å molecular sieves at 2–5 °C, routinely redistilled, and flushed with dry N_2 prior to use. Curox triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (a gift by Peroxid-Chemie GmbH, Munich, FRG) was our source of potassium peroxymonosulfate; it was used as received for the synthesis of dioxiranes **1a** and **1b**.

Solutions of 0.08–0.12 M dimethyldioxirane (**1a**)[4a-c] in acetone and of 0.8–1.0 M methyl(trifluoromethyl)dioxirane (**1b**)[4d,e] in TFP were obtained by adopting procedures, equipment, and precautions which have been described in detail.[4]

Reaction of commercial (Aldrich) acetophenone or 3-nitroacetophenone with phenylhydrazine gave the corresponding phenylhydrazones: **2a** (mp 103–105 °C)[20] and **2b** (mp 132–134 °C);[20] similarly, condensation of commercial phenylhydrazine, 4-nitrophenylhydrazine, or 2,4-dinitrophenylhydrazine with cyclohexanone in aqueous AcOH yielded derivatives **3a** (mp 81 °C),[20] **3b** (mp 146 °C; lit.[20] mp 147 °C), and **3c** (mp 162 °C),[20] respectively. Phenylhydrazone **4** (mp 191–192 °C; lit.[21a] mp 194 °C) was obtained upon reaction of $PhNHNH_2$ with 3α-acetoxy-5α-androstan-17-one (**5**): mp 163–164 °C [lit.[21b] mp 164.5–165.5 °C]; the latter derived from commercial *cis*-androsterone (Fluka) upon treatment with Ac_2O/py. 17β-Acetoxy-4-androsten-3-one tosylhydrazone (**6**) (mp 152–153 °C)[22] was obtained upon reaction of tosylhydrazine with commercial (Sigma) testosterone acetate (**7**) in acidic (AcOH) MeOH. Addition of *N,N*-dimethylhydrazine to cyclohexanone in presence of base (BaO) in EtOH yielded cyclohexanone dimethylhydrazone (**8**): bp 40 °C (10 mmHg); lit.[23] bp 65 °C (50 mmHg); MS (70 eV) *m/z* (r.i.) 140 (M^+, 44), 125 (15), 96 (24), 69 (31), 55 (23), 44 (100), 42 (58); IR (liquid film)

(19) By contrast, we find that dioxirane oxidation of a variety aldehyde hydrazones gives cleanly the corresponding nitriles in high yield. These results will be reported soon.

(20) Fourniss, B. S.; Vogel, A. I. *Textbook of Practical Organic Chemistry*, 5th ed.; Wiley: New York, 1989; pp 1336–1340.

(21) (a) Jacquignon, P.; Croisy-Delcey, M.; Croisy, A. *Bull. Soc. Chim. Fr.* **1972**, 4251. (b) vonEuw, J.; Reichstein, T. *Helv. Chim. Acta* **1942**, *25*, 988.

(22) Chandrasekhar, B. P.; Sunthankar, S. V.; Telang, S. G. *Chem. Ind. (London)* **1975**, 87.

(23) Karabatsos, G. J.; Taller, R. A. *Tetrahedron* **1968**, *24*, 3293.

1636 cm^{-1} (C=N). All starting materials above gave satisfactory ^1H and/or ^{13}C NMR spectra.

(+)-2*S*,2'*R*-2-(Methoxymethyl)-1-[(2'-methylcyclohexylidene)amino]pyrrolidine (9). By following closely a procedure described in detail by Enders et al.,[9] reaction of commercial (Aldrich) (−)-(*S*)-2-(methoxymethyl)pyrrolidine (SAMP) (0.98 g, 7.5 mmol) with racemic 2-methylcyclohexanone (0.84 g, 7.5 mmol) gave a mixture (1.6 g, 7.1 mmol, 95% yield) constituted largely by diastereomeric *E*-SAMP-hydrazones 2*S*,2'*R* and 2*S*,2'*S* in ca. 1:1 ration (by ^1H NMR[9b]). Column flash chromatography (silica gel, *n*-pentane/Et_2O 1:1) at subambient temperature (4–8 °C) afforded 0.9 g (4.0 mmol) of pure **10**: bp 155 °C (4 mmHg) [lit.[9a] bp 125 °C (0.06 mmHg)]; {^1H} ^{13}C NMR (100.56 MHz, $CDCl_3$) δ 17.46 (CH_3), 21.97, 24.23, 26.56, 27.08, 28.00, 35.14, 38.87, 54.96, 59.11 (OCH_3), 66.06, 75.44, 171.8 (*C*=N); ^1H NMR and MS spectra were in good agreement with literature[9a] data; FTIR (liquid film) 1626 cm^{-1} (C=N); $[\alpha]^{20}_D$ +218° (*c* 0.3, benzene) [lit.[9a] $[\alpha]^{20}_D$ +231° (*c* 1, benzene)].

Dioxirane Cleavage of Hydrazones. An aliquot (usually from 3 to 10 mL) normally containing 3 equiv of a standardized[4,5] cold solution of dimethyldioxirane (**1a**) (ca. 0.1 M in acetone) or of methyl(trifluoromethyl)dioxirane (**1b**) (ca. 0.8 M in TFP) was added to a stirred solution of 1 equiv of the hydrazone (100–500 mg) in acetone or CH_2Cl_2 (4–6 mL), kept at the given temperature (20 or 0 °C, cf. Table I). After the reaction was complete (GC/MS and/or TLC monitoring), product isolation was achieved upon removal of acetone solvent *in vacuo*, followed by column chromatography (silica gel, *n*-hexane/Et_2O or *n*-hexane/CH_2Cl_2). The ketone products were identified upon comparison of their physical constants and spectral characteristics (MS, FTIR, and/or ^1H NMR) with those of authentic samples (see above).

Cleavage of tosylhydrazone **6** had to be performed employing only 2 equiv of dioxirane **1a** in order to achieve high yield of unsaturated ketone **7** (Table I). When the reaction was carried out using 3 equiv of **1a**, the main product (yield ca. 75%) was epoxy ketone **4α,5-epoxy-17β-acetoxyandrostan-3-one**: mp 169–170 °C [lit.[24] mp 169.5–171 °C]; ^1H NMR (400 MHz, $CDCl_3$) δ 3.04 (s, 1 H, α-epoxide C^4-*H*), 4.62 (t, 1 H, *J* = 3 Hz, C^{17}-*H*-OAc), etc. (other resonances coincident with literature[24] data).

Column chromatography of the reaction mixture derived from oxidative scission of SAMP-hydrazone **9** gave, in addition to *R*-(−)-2-methylcyclohexanone (last entry, Table I), the nitrogen containing fragment **(−)-2-(methoxymethyl)-2-hydroxy-3,4-dihydro-2*H*-pyrrole (11)** (yield 30%): oil; ^1H NMR (400 MHz, C_6D_6) δ 1.34–2.28 (m, 4 H), 3.02 (s, 3 H, OCH_3), 3.80 (apparent q, 2 H, AB system, J_{AB} = 12 Hz, C*CH_AH_B OCH_3), 4.29 (s, 1 H, O*H*, exchangeable with D_2O), 5.14 (t, 1 H, *J* = 3 Hz, C*H*=N); {^1H}^{13}C NMR (100.56 MHz, $CDCl_3$) δ 15.96, 26.01, 57.61 (OCH_3), 74.06 (CH_2OCH_3), 90.46 (C^2), 156.5 (*C*=N); IR (liquid film) 3368 (OH), 2930, 2830, 1633 (C=N), 1451, 1245, 1101 cm^{-1}, etc.; $[\alpha]^{20}_D$ −2.6° (*c* 0.05, C_6D_6); using Eu(hftc)$_3$ in ^1H NMR polarimetry, downfield shift but *no splitting* is observed for the OCH_3 resonance; MS (EI, 70 eV) *m/z* (r.i.) 129 (M^+, 1), 128 (3), 115 (12), 113 (39), 87 (16), 85 (17), 83 (54), 82 (12), 80 (11), 71 (13), 78 (11), 57 (11), 56 (14), 55 (54), 54 (19), 45 (100), etc.; HRMS (CI, NH_3) found 130.0868 (M + H), calcd for $C_6H_{11}NO_2$ + H 130.0868.

Rate Measurements. By adopting a described[4e] competition kinetics technique, the two hydrazone substrates (**2a** = *A*, and **2b** = *B*) in the same solution were allowed to react with dioxirane **1a**, making $([A]_0 + [B]_0) > [\text{dioxirane}]_0$. With dimethyldioxirane **1a** initial concentration 0.2 × 10^{-2} M, and $[A]_0 = [B]_0 = 1.0 \times 10^{-2}$ M in acetone at 20 °C, aliquots were withdrawn at time intervals within the first 10–15% reaction and quenched with excess *i*-Bu_2S in $CHCl_3$ solution (also containing Freon A112 or C_6Cl_6 as GC calibration standard). The GC analyses of the samples allowed measurement of the relative rate as $(k^A/k^B) = \{\log([A]/[A]_0)/(\log([B]/[B]_0)\}$; the $\log([A]/[A]_0)$ vs $\log([B]/[B]_0)$ plots over five to six points were linear (*r* 0.99), yielding $k_r = (k^A/k^B) = 1.7$ (estimated error ≤ ±5%).

Acknowledgment. This work was supported in part by the Italian National Research Council (CNR, Rome) in the frame of the Progetto Finalizzato C.F.-II and by the Ministry of University, Scientific and Technological Research (MURST 40) of Italy. Work at Brown was supported by Interox R & D (Widnes, U.K.). Thanks are due to professor F. Ciminale for help in running and interpretation of EPR spectra and to Dr. J. van Epp (Brown U.) for NMR and HRMS spectra. A.A. is grateful for hospitality (September 1992–August 1993) to the Department of Chemistry of Brown University, a most gracious host institution.

(24) Koga, T.; Kawashima, S. *Chem. Pharm. Bull.* **1972**, *20*, 21.