JOC Notes

Magnesium/Methanol: An Effective Reducing Agent for Peroxides

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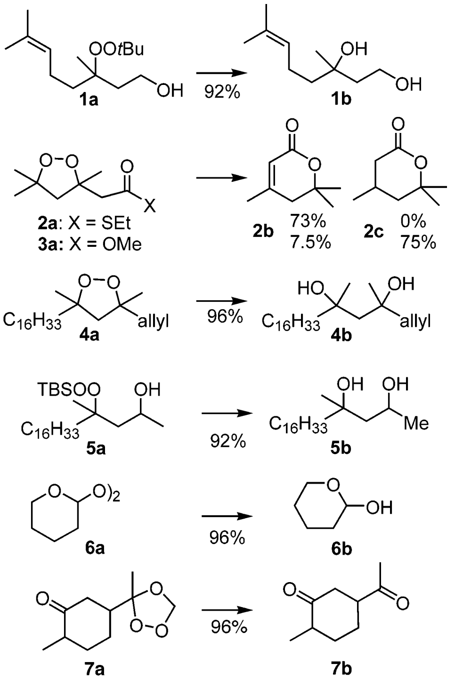
Abstract: Magnesium in methanol is an effective reagent for the chemoselective reduction of peroxides, including ozonides. Mg/MeOH is significantly more reactive than Me_2S or PPh_3 and somewhat more reactive than Zn/HOAc.

In the course of a synthetic approach to the plakinic acids, we required a mild method for reduction of 3,3,5,5-tetrasubstituted-1,2-dioxolanes. Dialkyl peroxides are reduced slowly by traditional reagents such as Me_2S or PPh_3.[1] Samarium iodide, which has been applied to reduction of 3,5-disubstituted-1,2-dioxolanes, proved ineffective toward our substrates.[2] Zn/HOAc is a well-known reagent for reduction of dialkyl peroxides,[1] but we were concerned about the compatibility of some of our anticipated substrates with the acidic conditions. We therefore investigated Mg/MeOH, a mild reagent that has been successfully applied to a number of chemoselective reductions.[3]

Our results are shown in Scheme 1. In a typical procedure, reaction is initiated by addition of magnesium turnings and a crystal of iodine to a solution of the peroxide in warm methanol. Following disappearance of the peroxide starting material,[4] the reactions were subjected to an aqueous workup and the crude products were purified by flash chromatography. The results demonstrate that Mg/MeOH effectively reduces dialkyl peroxides, dioxolanes, a silyl alkyl peroxide, a peroxyacetal, and an ozonide.

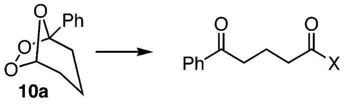
It is interesting to compare the reactivity of Mg/MeOH against more traditional reagents (Scheme 2). A bis *tert*-alkyl peroxide (**8a**) barely reactive toward Zn/HOAc is cleanly reduced by Mg/MeOH. Both Mg/MeOH and Zn/HOAc reduce dioxolane **9a**, which fails to react with Me_2S or PPh_3.

SCHEME 1. Reductions with Mg/MeOH[a]



[a] Mg (5.0 equiv), 40 °C, 3 h.

We were curious about the potential for magnesium alkoxide induced fragmentation of base-sensitive substrates. This concern proved well-founded as bicyclic ozonide **10a**, a substrate known to be particularly susceptible to base-mediated cleavage,[5] underwent reaction with Mg/MeOH to afford mainly the corresponding ketoacid (eq 1).



(1)

Reagent	**10b** (X =H)	**10c** (X = OH)	**10d** (X = OMe)
Zn/HOAc	86	8	0
Mg/MeOH	0	70	12

In conclusion, we have demonstrated that Mg/MeOH is a useful reagent for reduction of hindered peroxides or substituted ozonides.

Experimental Section

Standard experimental procedures are described elsewhere.[6] As with any investigations involving low molecular weight peroxides, experimenters are urged to follow standard safety precautions.[7]

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[2] Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989**, *30*, 6985–8.

[3] Zechmeister, L.; Rom, P. *Justus Liebigs Ann. Chem.* **1929**, *468*, 117–32. Profitt, J. A.; Watt, D. S.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 127–8. Brettle, R.; Shibib, S. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2912–19. Brown, A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749–50. Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409–10. Hutchins, R. O.; Suchismita; Zipkin, R. E.; Taffer, I. M.; Sivakumar, R.; Monaghan, A.; Elisseou, E. M. *Tetrahedron Lett.* **1989**, *30*, 55–6. Pak, C. S.; Lee, E.; Lee, G. H. *J. Org. Chem.* **1993**, *58*, 1523–30. Sridhar, M.; Vadivel, S. K.; Bhalerao, U. T. *Synth. Commun.* **1997**, *27*, 1347–50. Zarecki, A.; Wicha, J. *Synthesis* **1996**, 455–6. Sridhar, M.; Kumar, B. A.; Narender, R. *Tetrahedron Lett.* **1998**, *39*, 2847–50.

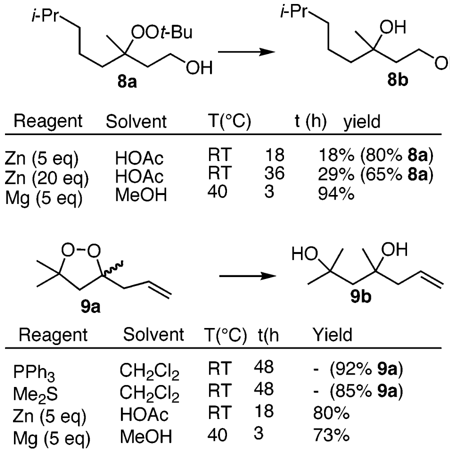
[4] Reactions were monitored with a redox-active TLC dip: Smith, L. L.; Hill, F. L. *J. Chromatogr.* **1972**, *66*, 101–9.

[5] Hon, Y.-S.; Lin, S.-W.; Lu, L.; Chen, Y.-J. *Tetrahedron* **1995**, *51*, 5019–34.

[6] Dussault, P. H.; Eary, C. T.; Woller, K. R. *J. Org. Chem.* **1999**, *64*, 1789–97.

10.1021/jo035191d CCC: $27.50

SCHEME 2. Comparison with Other Reducing Agents



Reagent	Solvent	T(°C)	t (h)	yield
Zn (5 eq)	HOAc	RT	18	18% (80% **8a**)
Zn (20 eq)	HOAc	RT	36	29% (65% **8a**)
Mg (5 eq)	MeOH	40	3	94%

Reagent	Solvent	T(°C)	t(h	Yield
PPh_3	CH_2Cl_2	RT	48	- (92% **9a**)
Me_2S	CH_2Cl_2	RT	48	- (85% **9a**)
Zn (5 eq)	HOAc	RT	18	80%
Mg (5 eq)	MeOH	40	3	73%

Mg/MeOH Reductions. To a solution of peroxide or ozonide (1 mmol) in MeOH (5 mL) was added freshly scratched Mg turnings and a tiny crystal of iodine. Warming the brown solution to 40 °C resulted in a rapid loss of color. Following consumption of the Mg (typically 3 h), the reaction mixture was cooled to 0 °C and diluted with ether (5 mL) and 10% aqueous NH_4Cl. The mixture was stirred until clear and then separated. The combined ether extracts (2 × 5 mL) were dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to chromatography through a plug of silica with ethyl acetate/hexane.

Zn/HOAc Reductions. To a room-temperature solution of peroxide or ozonide (1 mmol) in glacial acetic acid (5 mL) was added Zn powder (5 mmol). The reaction was stirred until the peroxide had disappeared (TLC). After dilution with water (5 mL) and ether (20 mL), the separated organic layer was washed with aqueous bicarbonate and worked up as before.

Acknowledgment. We thank the Petroleum Research Fund for generous support.

Supporting Information Available: References for preparation of starting materials; spectral listings and NMR (^{1}H and ^{13}C NMR) spectra for **4a**, **4b**, **5a**, **5b**, **8a**, **8b**, and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Patnaik, P. *A Comprehensive Guide to the Hazardous Properties of Chemical Substances*; Van Nostrand Reinhold: New York, 1992. Shanley, E. S. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 3, pp 341−69. Medard, L. A. *Accidental Explosions: Types of Explosive Substances*; Ellis Horwood Limited: Chichester, 1989; Vol. 2.