

## Convenient Oxidative Cleavage of Ethers by Metallic Nitrates Supported on Silica Gel

Takeshi Nishiguchi\* and Masahiro Bougauchi

Faculty of Liberal Arts, Yamaguchi University, Yamaguchi 753, Japan

Received April 24, 1989

**Summary:** Several metallic nitrates supported on silica gel efficiently cleaved and oxidized primary and secondary ethers to the corresponding aldehydes and ketones. Especially,  $\text{Cu}(\text{NO}_3)_2$  and  $\text{Zn}(\text{NO}_3)_2$  are suitable for practical use. Silica gel was essential for the efficient oxidation. Overoxidation of the formed aldehydes to carboxylic acids was not observed. This ether oxidation seems to be useful for organic synthesis because of easy experimental operations, high yields of products, and mild reaction conditions. Some mechanistic studies suggest that the key step of the process involves the formation of radical species.

**Sir:** Reactions utilizing reagents or reactants on insoluble inorganic supports often have advantage of ease of set up and workup, mild conditions, and increased yields compared with their homogeneous counterparts.<sup>1</sup> In the course of studying oxidation of alcohols by metallic nitrates supported on silica gel,<sup>2</sup> we have found ethers too are oxidized by these reagents. This oxidative cleavage of ethers to give aldehydes or ketones seems to be useful for organic synthesis because the ease of experimental operations, high yields of products, and mild reaction conditions. Diethyl ether has been reported to react with  $\text{Cu}(\text{NO}_3)_2$  to give a trace of acetaldehyde,<sup>3</sup> and a few other studies have been reported<sup>4</sup> on one-step oxidation of ethers to aldehydes and ketones.

The oxidizing reagents (abbreviation;  $\text{M}(\text{NO}_3)_n\text{-SiO}_2$ ) were prepared by the method previously reported.<sup>2</sup> Unless otherwise noted, the oxidation reaction in this study was carried out by heating an ether (1 mmol) and a nitrate reagent (4 mmol; 3.5 mmol per gram of  $\text{SiO}_2$ ) in refluxing  $\text{CCl}_4$  or isooctane (20 mL) under nitrogen. Brown gas appeared in the reaction vessel when the oxidation started and disappeared when completed. Therefore, the reaction can be monitored by checking the amount of the gas. The reaction solution was separated from the solid reagent by filtration and submitted to GC and/or  $^1\text{H}$  NMR analysis after the addition of an internal standard. Eluting the isolated solid with acetone or  $\text{CCl}_4$  usually gave additional amounts of the products and the recovered alcohols. The elution was always performed to improve material balance in this study.

Oxidation of several ethers was studied using  $\text{Cu}(\text{NO}_3)_2\text{-SiO}_2$ , which, as well as  $\text{Zn}(\text{NO}_3)_2\text{-SiO}_2$ , is active,

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(2) (a) Nishiguchi, T.; Asano, F. *Tetrahedron Lett.* 1987, 28, 4565. (b) Nishiguchi, T.; Asano, F. *J. Org. Chem.* 1989, 54, 1531. Therein the reports of Laszlo et al. concerning oxidation of alcohols by clay-supported metallic nitrates are cited.

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Table I. Oxidative Cleavage of Ethers by  $\text{Cu}(\text{NO}_3)_2\text{-SiO}_2^a$ 

ether	solvent	yield and recovery, %	
		product	ether
benzyl methyl ether	isooctane	benzaldehyde, 91	0
benzyl isoamyl ether	isooctane	benzaldehyde, 85 2-methylbutanal, 26	2
cyclododecyl methyl ether	isooctane	cyclododecanone, 84	11
hexyl ether	isooctane	hexanal, 104 <sup>b</sup>	39
hexyl ether	$\text{CCl}_4$	hexanal, 53 <sup>b</sup> hexyl nitrite, 12	40
benzyl ethyl ether	$\text{CCl}_4$	benzaldehyde, 85 ethyl nitrite, 30	3
benzyl hexyl ether	$\text{CCl}_4$	benzaldehyde, 79 hexyl nitrite, 68	22
benzyl cyclohexyl ether	$\text{CCl}_4$	benzaldehyde, 91 cyclohexanone, 35 cyclohexyl nitrite, 1	0
benzyl ether	$\text{CCl}_4$	benzaldehyde, 187 <sup>b</sup>	0
2-hexenyl methyl ether	$\text{CCl}_4$	2-hexenal, 90	0

<sup>a</sup> Reaction time was 1 h. <sup>b</sup> One mole of the product from 1 mol of the ether was calculated as 100%.

Table II. Oxidative Cleavage of Benzyl Cyclohexyl Ether by Metallic Nitrates Supported or Not Supported on Silica Gel<sup>a</sup>

nitrate	yield and recovery, %		ether
	benzaldehyde	cyclohexanone	
$\text{Cu}(\text{NO}_3)_2$	94	27	0
$\text{Cu}(\text{NO}_3)_2^b$	70	33	18
$\text{Cu}(\text{NO}_3)_2^{b,c}$	8	4	91
$\text{Cu}(\text{NO}_3)_2^{b,d}$	34	18	60
$\text{Zn}(\text{NO}_3)_2$	94	24	0
$\text{Zn}(\text{NO}_3)_2^b$	60	32	19
$\text{Zn}(\text{NO}_3)_2^{b,c}$	4	1	95
$\text{Zn}(\text{NO}_3)_2^{b,d}$	25	13	70
$\text{Bi}(\text{NO}_3)_3$	84	29	0
$\text{Ce}(\text{NO}_3)_3$	75	42	15
$\text{Co}(\text{NO}_3)_2$	69	29	14
$\text{Fe}(\text{NO}_3)_3$	58	12	29
$(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$	26	14	73

<sup>a</sup> The reactions were carried out in isooctane for 1 h. <sup>b</sup> The reaction in  $\text{CCl}_4$  for 1.5 h. <sup>c</sup> Silica gel was not used. <sup>d</sup> This reaction was carried out under oxygen.

thermostable at reaction temperatures, inexpensive, able to be kept in dry air without losing its activity, and of low toxicity for human body and environment. Primary and secondary ethers gave the corresponding aldehydes and ketones in high yields (Table I). Relative reaction rates of 2-hexenyl, benzyl, cyclododecyl, and nonyl methyl ethers were found to be 184:89:32:1 in the oxidation by  $\text{Cu}(\text{NO}_3)_2\text{-SiO}_2$  in  $\text{CCl}_4$ . Nitrites too were isolated when they were stable and reaction temperatures were low. These nitrites are inferred to give the carbonyl compounds from the result that cyclohexyl nitrite gave cyclohexanone in 88% yield on being heated in  $\text{CCl}_4$  for 15 min in the presence of 2 equiv of  $\text{Cu}(\text{NO}_3)_2\text{-SiO}_2$  while it scarcely reacted in the presence of  $\text{Cu}(\text{NO}_3)_2$  or silica gel only. Overoxidation of the formed aldehydes to the corresponding carboxylic acids was not observed in any case.

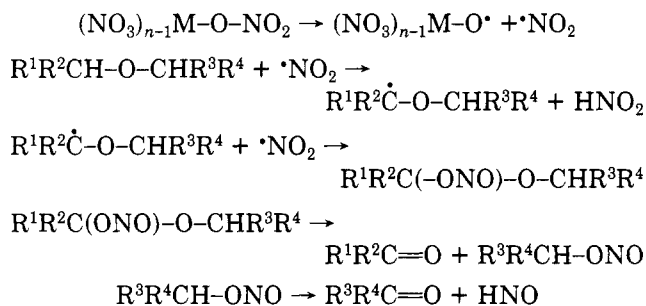
The activity of several metallic nitrates was investigated and a part of the results are shown in Table II. Nitrates of Cu(II) and Zn(II) were most active, and those of alkali and alkaline earth metals were hardly active. The tendency that covalent nitrites were more reactive than ionic

nitrates is in accordance with the tendency reported in the oxidation of a few organic compounds.<sup>5</sup> The activity of the nitrates that had been powdered and dried but not supported was found to be very low (Table II). This result indicates the necessity of silica gel for the satisfactory oxidation.

The activity of some solid supports was examined in the reaction of  $\text{Zn}(\text{NO}_3)_2$  and found to decrease in the order: silica gels (Merck and Fuji-Davidson, 230-300 mesh) > alumina (ICN, N-super I) > bentonite clay. Molecular sieves 3A (powder), zeolite A-4 (synthetic, 200 mesh), Celite 535, and active carbon (powder) were ineffective. This result suggests that the main function of silica gel is not to widen the surface area of metallic nitrates. Silica gel is speculated to promote the oxidation by forming a special reaction field where reagents and substrates are accumulated by adsorption and activated by hydroxyl groups of the support.

We would like to propose a radical mechanism for the oxidative cleavage of ethers by  $\text{Cu}(\text{NO}_3)_2$ - and  $\text{Zn}(\text{NO}_3)_2$ - $\text{SiO}_2$  on the following grounds. (1) By changing the atmosphere from nitrogen to oxygen the oxidation was suppressed (Table II). The inhibiting effect of oxygen may be explained by the presumption that the oxidation involves radicals, because radical reactions are generally influenced by the presence of oxygen. (2) The brown gas that appeared during the oxidation seems to be  $\text{NO}_2$ , which is a radical. (3) The yield of benzaldehyde and cyclohexanone was reduced to about half by the addition of 15 mol % (to  $\text{Cu}(\text{NO}_3)_2$ ) of 2,6-tri-*tert*-butylphenol, which is a sterically hindered radical scavenger, in the 15-min reaction of  $\text{Cu}(\text{NO}_3)_2$ - $\text{SiO}_2$  in  $\text{CCl}_4$ . The weakness of the inhibiting effect of the phenol may be explained by the speculation that the phenol and  $\text{NO}_2$  are adsorbed and fairly fixed on the surface of silica gel. (4) Nitrites were sometimes isolated. (5) The logarithm of initial rates in the oxidation of *p*-methyl-, *p*-fluoro-, *p*-chloro-, and *p*-

nitrobenzyl methyl ethers by  $\text{Cu}(\text{NO}_3)_2$ - $\text{SiO}_2$  in  $\text{CCl}_4$  linearly depended on the Hammett substituent constants to give  $-0.31$  as the value of  $\rho$ . The result that the electronic character of the substituents influence the reaction rates but little suggests, though not clearly, that radicals rather than ions are formed as intermediates. (6) The ratio of the initial rate of the oxidation of benzyl methyl ether to that of the ether in which  $\alpha$ -hydrogens of the benzyl group had been replaced by deuterium ( $k_{\text{H}}/k_{\text{D}}$ ) was 2.7 in the reaction of  $\text{Cu}(\text{NO}_3)_2$ - $\text{SiO}_2$  and 3.1 in the one of  $\text{Zn}(\text{NO}_3)_2$ . This result suggests that the cleavage of the bond between the hydrogens and  $\alpha$ -carbon of the benzyl group is the rate-determining step. (7) Some kinds of esters, halides, and amines were also oxidized by the supported reagents.<sup>6</sup> The observations described above are compatible with a radical pathway. Therefore, we would like to propose the following scheme for this oxidation. The formation of  $\text{NO}_2$



from metallic nitrates has been reported.<sup>5</sup> Further, it is noteworthy that  $\text{N}_2\text{O}_4$ , which is usually equilibrated with  $\text{NO}_2$ , has been reported to oxidize some kinds of organic compounds.<sup>7</sup> Chlorinated products were not detected in the reactions in  $\text{CCl}_4$ . This fact may be explained at least partly by the weak tendency of the solvent to be adsorbed on silica gel surface where the oxidation seems to take place.

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(6) The study of these reactions is now progressing.

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## Acyclic Stereoselection in the Alkylation of Chiral Dipole-Stabilized Organolithiums: A Self-Immolative Chirality Transfer Process for the Synthesis of Primary Amines<sup>1</sup>

Robert E. Gawley,\* Kathleen Rein, and Sanjay Chemburkar

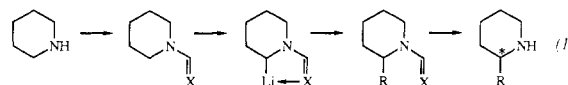
Department of Chemistry, University of Miami, Coral Gables, Florida 33124

Received March 8, 1989

**Summary:** A comparison of 1,3- and 1,5-asymmetric induction shows the former to have far greater selectivity in the methylation of chiral dipole-stabilized organolithiums. The asymmetric alkylation of *N*-benzyl-oxazolidinones is employed as the key step in a new synthesis of primary amines by asymmetric alkylation  $\alpha$  to nitrogen.

**Sir:** The elaboration of nitrogen heterocycles by alkylation  $\alpha$  to nitrogen (eq 1) is firmly established as a useful method in organic synthesis.<sup>2</sup> In that the process generates a

stereocenter (\*), a useful and important amplification of the sequence is its application to the preparation of enantiomerically pure compounds. This has been accom-



plished in two strategically different ways: the use of a chiral auxiliary attached to nitrogen,<sup>3</sup> and by use of a chiral

(1) K.R. thanks the University of Miami for a Maytag Fellowship, 1987-90. We are grateful to the National Institutes of Health for financial support: Grant GM-37985 supported this work and Grant RR-03351 provided funds for the purchase of the 400-MHz NMR.

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