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A NOVEL RING CLEAVAGE REACTION OF OXAZOLINES

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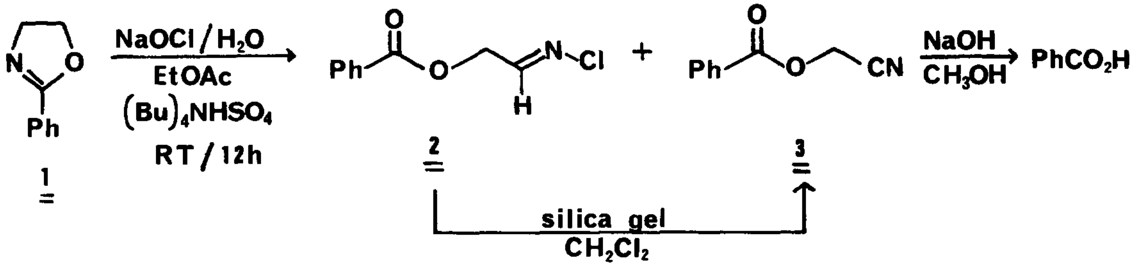
Summary: An oxazoline can be cleanly converted to the parent carboxylic acid by treatment with NaOCl, followed by mild basic hydrolysis of the intermediate ester product(s).

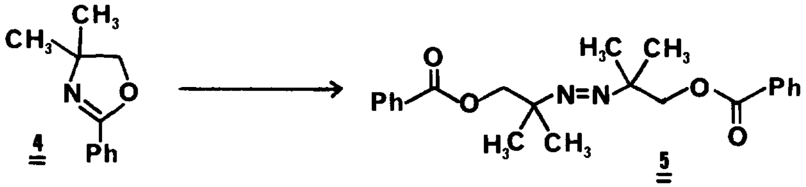
Oxazolines are now generally recognized as highly versatile synthons in organic chemistry. These readily available heterocycles are effective as carboxylic acid protecting groups,[2] and as activators both for various metalation reactions[1,3] and for aromatic nucleophilic substitutions.[4] Chiral oxazolines have recently played an important role in synthesis of many types of optically active compounds.[4c,d,5,6] An important feature of oxazolines is that they can be converted back to the carboxylic acid from which they were initially derived by either an acidic hydrolysis or by N-methylation followed by a basic hydrolysis.[1] In this paper we report a new oxidative ring cleavage reaction of oxazolines which we have developed into a mild, convenient transformation of these compounds to the parent carboxylic acid. This method may prove to be a useful alternative to the aforementioned hydrolysis procedures.

We discovered that treatment of oxazoline 1 with commercial laundry bleach (5.25% sodium hypochlorite solution) in ethyl acetate under phase transfer conditions at room temperature affords about a 1:1 mixture of N-chloroimino-ester 2 and nitrile 3 in high yield. As one might expect,[7,8] 2 is rather unstable and can be cleanly converted to 3 upon stirring in CH_2Cl_2 containing some silica gel. This ring cleavage is highly solvent dependent. In ethyl acetate conversion of 1 to 2 + 3 is reasonably rapid, but in methylene chloride the reaction is ex-

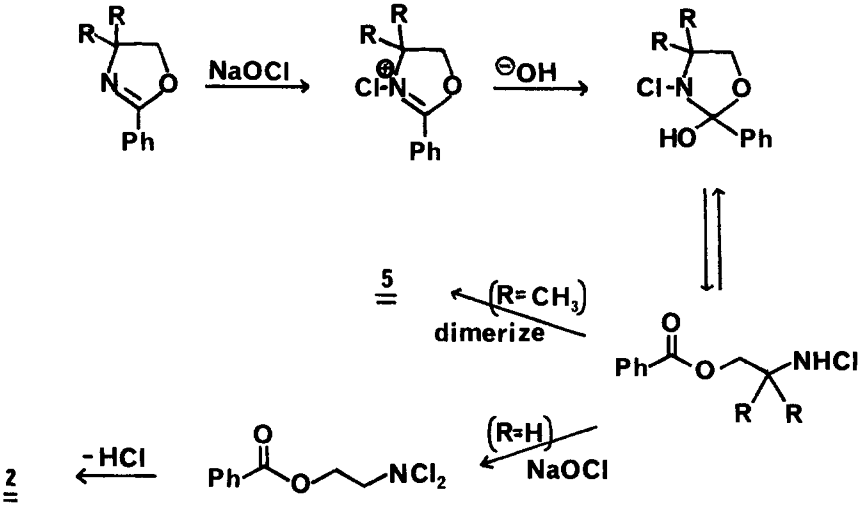


tremely slow. No reaction occurs under homogeneous conditions in THF. A very similar solvent dependence has been reported for NaOCl oxidations of amines and alcohols.[7] Basic hydrolysis of the crude mixture of 2 and 3 afforded benzoic acid.

Interestingly, treatment of oxazoline 4 with NaOCl under identical conditions provides diazo-ester 5 which is sufficiently stable to be purified by chromatography on silica gel.[8]



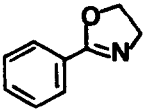
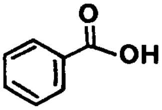
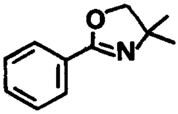
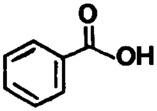
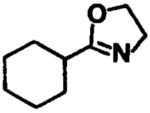
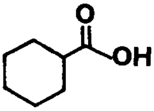
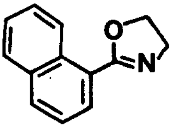
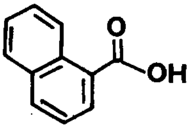
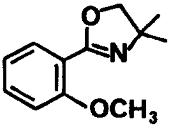
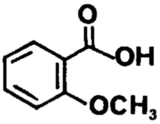
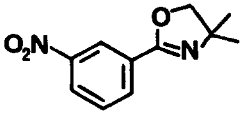
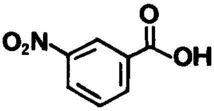
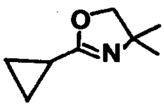
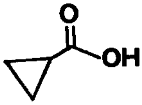
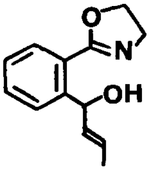
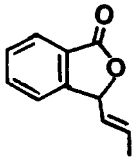
A reasonable mechanism for the conversion of oxazolines to products of type 2 and 5 is shown in the Scheme, although other mechanistic variations for this novel ring cleavage are quite possible. Dimerization of tertiary N-haloamines to azo-compounds is well precedented[8] as is the conversion of primary and secondary amines to N-chloroimines by hypochlorite.[7]



Combination of this hypochlorite induced ring opening reaction with a subsequent mild basic ester hydrolysis using methanolic sodium hydroxide has been found to be a good "one-pot" method for preparation of carboxylic acids from various types of oxazolines. A general experimental procedure is outlined below. We have applied this method to the oxazolines listed in the Table, and as can be seen, isolated yields of the resulting carboxylic acids are good. Intermediate esters were not characterized in these cases.

General Procedure for Conversion of Oxazolines to Carboxylic Acids: To a solution of 1.0 mmol of oxazoline in 10 mL of ethyl acetate was added 0.034 g (0.1 mmol) of tetrabutylammonium bisulfate and 17 mL of 5.25% aqueous sodium hypochlorite solution. The mixture was stirred at room temperature until TLC indicated disappearance of starting material (12-48h).

Table Preparation of Carboxylic Acids from Oxazolines

Entry	Oxazoline	Product	Isolated Yield (%)
1			89
2			92
3			76
4			79
5			84
6			93
7			60 [9]
8			80[10]

The aqueous layer was acidified with 5% HCl, and was extracted twice with ethyl acetate. The original organic layer and the organic extract were combined and concentrated to a small volume *in vacuo*. To the residue was added 5 mL of methanol and 15 mL of 5% NaOH. The mixture was stirred at room temperature for 5 h and was extracted with ethyl acetate. The aqueous phase was acidified with 5% HCl, and was extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and evaporated to afford nearly pure carboxylic acid.

Acknowledgments

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(9) Yield estimated by NMR analysis. The product was contaminated with some acetic acid which proved difficult to remove.

(10) The base hydrolysis was omitted in this reaction.

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