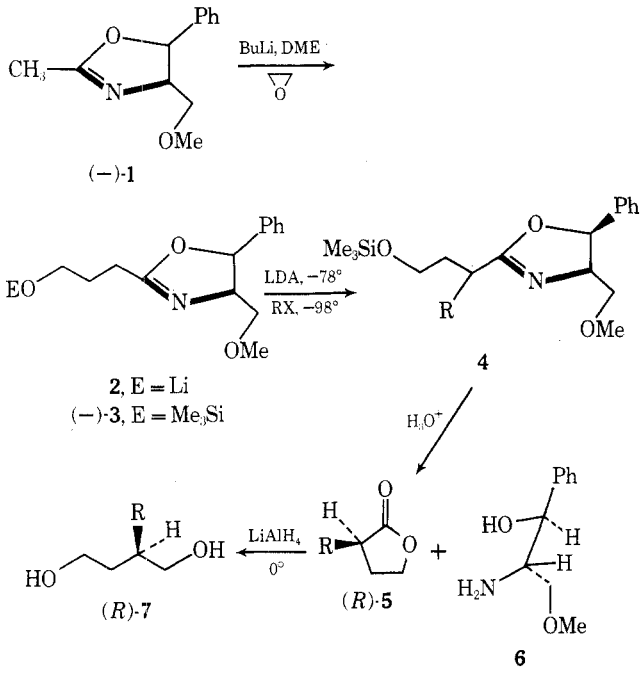
Table I
Asymmetric Synthesis of (*R*)-γ-Butyrolactones 5 and (*R*)-1,4-Butanediols 7

Compd	R	Yield, %[a]	$[\alpha]^{23}_{589}$ (cEtOH)	Optical purity, %	CD, $[\theta]_{218\ nm}$ (CH_3CN)
(*R*)-5	Me	58	+13.80 (10.0)	64.2[b]	−1430[g]
(*R*)-5	Et	68	−7.65 (9.8)		−1750
(*R*)-5	*n*-Pr	75	−8.05 (5.7)	73.3[c]	−1870
(*R*)-5	Allyl	60	−16.50 (4.8)	72.0[c]	−1730
(*R*)-5	*n*-Bu	71	−7.30 (9.7)		−1600
(*R*)-7	*n*-Pr	90[d]	+3.47 (neat)	73.3[e]	
(*R*)-7	Allyl	92[d]	+3.60 (neat)	72.0[f]	

[a] Yields of 5 based upon 3 unless otherwise noted. [b] T. Kaneko, K. Wakabayashi, and H. Katsura [*Bull. Chem. Soc. Jpn.*, 35, 1149 (1962)] report $[\alpha]^{15}D$ −21.5 (c 5.5, EtOH). [c] Based upon the optical purity of the corresponding 1,4-butanediols 7 which must be a minimum value since some racemization of 5 during the reduction is possible. [d] Based upon 5. [e] Literature value[5] +4.73° (neat). [f] Literature value[5] +5.0° (neat). [g] Molecular ellipticities were determined on a Varian-Cary Model 61 CD instrument. Units are degrees centimeter squared/decimole.



γ-butyrolactones **5**, all of which possessed the *R* configuration (Table I).[4] Since the absolute configuration and maximum rotation was known only for 2-methyl-γ-butyrolactone (**5**, R = Me), and a variety of chiral shift reagents failed to provide enantiomeric compositions for the lactones, it was necessary to correlate **5** by other methods. This was readily done by reducing ($LiAlH_4$, 0°, Et_2O) the 2-(*n*-propyl)- and 2-allylbutyrolactones to their corresponding 1,4-butanediols **7** which had been previously described by Freudenberg and Lwowski.[5] The facile conversion of **5** to **7** now makes chiral 1,4-butanediols readily accessible in optical purity comparable to those of the lactones. Furthermore, since the lactones **5** were all of the *R* configuration, as indicated by their comparable CD characteristics, the diols (+)-**7** can now be assigned the *R* configuration.[6]

The production of *R* lactones via this method is consistent with the mechanism proposed in our earlier report.[1] Reversal of the order of introduction of substituents on (−)-**1** would presumably lead to the *S* lactones. Work is continuing toward further utility of this asymmetric synthesis and the potential incorporation of chiral 1,4-butanediols as precursors to chiral polyethers and polyesters.

Acknowledgment. Financial support from the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

References and Notes

(1) A. I. Meyers and G. Knaus, *J. Am. Chem. Soc.*, **96**, 6508 (1974). The efficiency of this asymmetric synthesis has since been increased to over 80% routinely by further modifications in procedure. This will be described in the full paper at a future date.
(2) A. I. Meyers, G. Knaus, and K. Kamata, *J. Am. Chem. Soc.*, **96**, 268 (1974).
(3) Saturated alkyl groups were all introduced as their iodides, allylic and benzyl groups were added as the chlorides, while methyl was added as methyl sulfate (cf. ref 1).
(4) Metalation of the lithio salt **2** (E = Li) to the dilithio salt also gave alkylation upon addition of 1.0 equiv of alkyl halide. Hydrolysis to the lactone **5** proceeded smoothly; however, the optical purity was only 10–12%.
(5) K. Freudenberg and W. Lwowski [*Justus Liebigs Ann. Chem.*, **594**, 76 (1955)] prepared **7** (R = *n*-propyl, allyl) by reduction of the corresponding succinic acids which were obtained by resolution. No absolute configurations were reported by these authors.
(6) R. Rossi, P. Diversi, and G. Ingrosso [*Gazz. Chim. Ital.*, **48**, 1391 (1968)] have correlated (*R*)-(+)-2-methylsuccinic ester with (*R*)-(+)-2-methyl-1,4-butanediol.
(7) Eastman Kodak Fellow, 1974–1975.

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A Rapid Procedure for the Hydrolysis of Amides to Acids

Summary: The hydrolysis of amides to acids by aqueous sodium peroxide (in less than 2 hr at 50–80°) in high yield and with little decarboxylation of the acid is reported.

Sir: The conversion of amides to carboxylic acids is considered a routine procedure but in practice it is not always straightforward.[1] Often vigorous conditions[2] and strong catalysts such as concentrated sulfuric or phosphoric acid[3] and strong alkali hydroxides are needed to effect the hydrolysis. In general, the yields of these reactions are fair to good but occasionally the severe reaction conditions cause decomposition of the desired acid. For example, we have found that the usual hydrolytic conversions of heterocyclic carboxamides to the corresponding acids are particularly difficult because the acids are prone to decarboxylation. To circumvent this problem a new method was developed. Specifically, we have found sodium peroxide (caution—see final paragraph for warning for using peroxides) to be a superior reagent for the mild hydrolysis of heterocyclic amides and other amides in general. The reaction is rapid and can be carried out at relatively low temperatures. We would like to recommend it as a simple, nonstringent general procedure.

Table I
Yields of Acid from the Hydrolysis of Amides with Sodium Peroxide

Amide	Acid isolated	Amine isolated	Absolute yield, %
$C_6H_5CONH_2$	$C_6H_5CO_2H$		85
$3\text{-}CH_3OC_6H_4CONH_2$	$3\text{-}CH_3OC_6H_4CO_2H$		81
$4\text{-}CH_3OC_6H_4CONH_2$	$4\text{-}CH_3OC_6H_4CO_2H$		88
$2,6\text{-}(CH_3)_2C_6H_3CONH_2$	$2,6\text{-}(CH_3)_2C_6H_3CO_2H$		88
$C_6H_4\text{-}1,3\text{-}(CONH_2)_2$	$C_6H_4\text{-}1,3\text{-}(CO_2H)_2$	NH_3	95
$C_6H_5CH_2CONH_2$	$C_6H_5CH_2CO_2H$		94
2-Pyrazinamide	2-Pyrazinoic acid		81
3-Hydroxy-2-pyrazinamide	3-Hydroxy-2-pyrazinoic acid		73
2-Picolinamide	2-Picolinic acid		89
$C_{11}H_{23}CONH_2$	$C_{11}H_{23}CO_2H$		83
$(CH_3)_2CHCONH_2$	$(CH_3)_2CHCO_2H$		78
$CH_3CONHC_6H_5$		$C_6H_5NH_2$	89
$C_6H_5CONHCH_3$	$C_6H_5CO_2H$		83
$C_{11}H_{23}CONH\text{-}n\text{-}C_4H_9$	$C_{11}H_{23}CO_2H$		87
$CH_3CON(CH_3)C_6H_5$		$C_6H_5NH(CH_3)$	89
$C_6H_5CONHC_6H_5$			No reaction
$C_6H_5CON(CH_2CH_3)_2$			No reaction

$$R\text{—}\overset{\overset{O}{\|}}{C}\text{—}NHR' + Na_2O_2 \xrightarrow{H_2O} \xrightarrow{HCl} RCO_2H + R'NH_2$$

An aqueous suspension of the amide is treated with 1 equiv of sodium peroxide at 50° (or more conveniently on a steam bath). The amide rapidly dissolves and ammonia (for primary amides) is evolved. After 60 min, the reaction is essentially complete and only marginal yield increases are observed if heating is continued for another hour. Isolation of the acid is accomplished by careful neutralization of the reaction mixture and yields are usually greater than 85% (Table I). Primary, secondary, and tertiary amides are all hydrolyzed and either the acid or the amine can be recovered. Only extremely water-insoluble amides failed to react and, although ethanol can be substituted as solvent for some of the reactions, it was of no value in these cases. This appears to be the only restriction on the generality of the reaction. Very little decomposition of any of the acids was observed. The high yields for 2-pyrazinoic acid, 3-hydroxy-2-pyrazinoic acid, 2-picolinic acid, and 2,6-dimethylbenzoic acid should be especially noted since these acids are difficult to obtain in good yields from their amides by conventional hydrolysis methods.

The mechanism of the reaction has not been elucidated but the consumption of peroxide corresponds to the yield of acid (see Table II). One equivalent of peroxide is necessary to give complete hydrolysis and decreasing peroxide gives a proportionate decrease in yield. Peroxides have not been used to hydrolyze amides previously although hydrogen peroxide was suggested as a method to digest proteins.[4] A mechanism was not discussed but it may be that the α effect[5] makes the peroxide ion extremely nucleophilic, increasing the rate of reaction with the poorly electrophilic amide carbonyl groups. We have prepared the corresponding peroxycarboxylates and found them to decompose cleanly to the acid at the temperatures involved. Because of the known oxidizing power of peroxides, it might alternately be suggested that an oxidative hydrolysis is involved. Nitriles can be hydrolyzed to hydroxamic acids and thence to carboxylic acids with hydrogen peroxide.[6] A similar process could be occurring with sodium peroxide. However, nitrobenzene is derived from the amine portion of *N*-phenylamides when treated with hydrogen peroxide[7] and other amides show extensive degradation of the amine.[8] In all of our examples either ammonia (as opposed to hydroxylamine) or the amine from secondary or tertiary amides was isolated. Other oxidative mechanisms may be occurring but without further data we favor accelerated hydrolysis as the most plausible explanation at this time.

$$R\text{—}\overset{\overset{O}{\|}}{C}\text{—}NH_2 + HO_2^- \longrightarrow R\text{—}\overset{\overset{O^-}{|}}{\underset{\underset{O\text{—}OH}{|}}{C}}\text{—}NH_2 \longrightarrow R\text{—}\overset{\overset{O}{\|}}{C}\text{—}O_2^- + NH_3$$

Table II
Comparison of Reaction Time, Yield, and Loss of Peroxide for Benzamide and Sodium Peroxide

Time, min.	Acid yield, %[a]	Peroxide remaining, %
15	32	43
30	52	11
45	70	1
60	87	0
120	94	0

[a] Acid yield is amount isolated which could lag behind conversion as indicated by loss of peroxide.

The following example for pyrazinamide will illustrate the general procedure. Pyrazinamide (2.0 g, 0.0165 mol) is suspended in 50 ml of water and the mixture placed on the steam bath. Sodium peroxide (1.29 g, 0.0165 mol) is then added portionwise with care [the reaction of sodium peroxide with water can be exothermic and reactions reminiscent of metals in water have been observed with large-scale mixtures (>1 mol) of amides and sodium peroxide]. Ammonia can be detected being evolved with a piece of moist pH paper. After heating for 2 hr, the resulting solution is cooled to 0° and carefully acidified dropwise with concentrated hydrochloric acid. The crystals are separated by filtration to yield 1.9 g (94.2%) of pyrazinoic acid, mp 222–225° (lit.[9] mp 225°).

As in all reactions involving peroxides and organic compounds, caution should be exercised and all new reactions performed first on a small scale. No serious incidents occurred in any of the reactions that we have run but the observation of a transitory metalloid-type intermediate dictates that utmost safety precautions be followed.

References and Notes

(1) B. C. Challis and J. A. Challis, in "The Chemistry of Amides", J. Zabicky, Ed., Interscience Publishers, New York, N.Y., 1970, Chapter 13, p 816 ff.
(2) S. R. Sandler and W. Karo, "Organic Functional Group Preparations", Academic Press, New York, N.Y., 1972, Chapter 9, p 230.
(3) C. Berger and S. C. J. Olivier, *Recl. Trav. Chim. Pays-Bas*, **46**, 600 (1927).
(4) N. O. Sieber, *Z. Physiol. Chem.*, **81**, 185 (1913); *Chem. Abstr.*, **7**, 1028.
(5) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).
(6) E. Oliveri-Mandala, *Gazz. Chim. Ital.*, **52** (I), 107 (1922); *Chem. Abstr.*, **16**, 2112.
(7) H. Ito, *Chem. Pharm. Bull. Jpn.*, **12** (3), 326–329 (1964).
(8) B. C. Challis and J. A. Challis, ref 1, p 790.
(9) S. A. Hall and P. E. Spoerri, *J. Am. Chem. Soc.*, **62**, 664 (1940).

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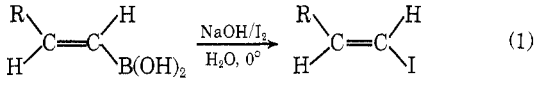
Reaction of Alkenylboronic Acids with Bromine in the Presence of Sodium Methoxide and Methanol. A Simple One-Stage Synthesis of α-Bromo Acetals

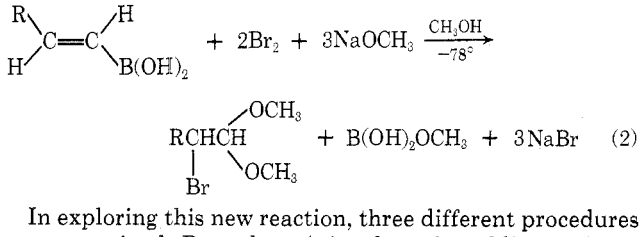
Summary: Alkenylboronic acids add bromine rapidly at −78° in the presence of sodium methoxide in methanol to give the corresponding α-bromo dimethyl acetals in good yield.

Sir: Alkenylboronic acids are readily available via the hydrolysis of the catechol esters produced by the hydroboration of alkynes with catecholborane.[1] We recently reported that such *trans*-1-alkenylboronic acids are converted by iodine under the influence of base into the corresponding *trans*-1-alkenyl iodides of >99% stereochemical purity in almost quantitative yield[2] (eq 1).



(1)

We undertook to prepare the corresponding bromides by an analogous procedure using bromine. However, the results proved unsatisfactory. For example, the addition of bromine to a solution of *trans*-1-octenylboronic acid in aqueous sodium hydroxide at 0° gave a 65:35 mixture of *cis*- and *trans*-1-octenyl bromide in a yield of ~50%, along with 25% *n*-octylaldehyde. A possible route to the aldehyde is oxidation of the vinylboronic acid by sodium hypobromite.[3] Consequently, we examined the use of sodium methoxide in methanol at −78° as a means of avoiding this side reaction.[2] Unexpectedly, the reaction produced 38% new product, the α-bromo dimethyl acetal, together with 8% *cis*-1-octenyl bromide and 10% *trans*-1-octenyl bromide. It seems clear that the formation of the α-bromo dimethyl acetal will require at least 3 equiv of sodium methoxide and 2 equiv of bromine (eq 2).



(2)

In exploring this new reaction, three different procedures were examined. Procedure A involves the addition of two equivalents of bromine in dichloromethane to a solution of *trans*-1-octenylboronic acid and 3 equiv of sodium methoxide in methanol at −78°. Procedure B involves the addition of *trans*-1-octenylboronic acid to a solution of 2 equiv of bromine and 3 equiv of sodium methoxide in methanol at −78°. Procedure C involves the addition of a cold solution of *trans*-1-octenylboronic acid and a 1 *M* equiv of sodium methoxide in methanol to a solution of 2 equiv of bromine and 2 equiv of sodium methoxide in methanol at −78°. The results are summarized in Table I.

Table I
Reaction of *trans*-1-Octenylboronic Acid with Bromine in the Presence of Sodium Methoxide at −78°

Procedure	α-Bromo acetal, %	*cis*-1-Octenyl bromide, %	*trans*-1-Octenyl bromide, %
A	80	2	16
B	63	19	16
C	92	0	4

Bromination of a series of *trans*-1-alkenylboronic acids was carried out by procedure C to produce the corresponding α-bromo dimethyl acetals. The results are summarized in Table II.

Table II
Preparation of α-Bromo Acetals by the Bromination of *trans*-1-Alkenylboronic Acids in the Presence of Sodium Methoxide at −78°

Alkyne	Alkenylboronic acid, %[a]	α-Bromo dimethyl acetal, %[b]
1-Hexyne	90	92,[c] 82[d]
1-Octyne	90	92,[c] 82[d] (72,[c] 55[d])
3-Chloro-1-pentyne	92	90,[c] 82[d]
Cyclohexylethyne	93	88,[c] 81[d]
3,3-Dimethylbutyne	94	52,[c] 49[d]

[a] See ref 1. Isolated yields. [b] The yields are by GLPC analysis. The values in parenthesis are isolated yields. [c] Based on alkenylboronic acid. [d] Based on alkyne.

One exception to the generality of this procedure was observed. *trans*-2-Phenyl-1-ethyleneboronic acid was converted by procedure C to give a product which was not the 2-bromo acetal. This product is under investigation.

The following experimental procedure (procedure C) was used. In a 250-ml flask were placed 100 mmol of *trans*-1-octenylboronic acid[1] and 100 ml of absolute methanol; 100 mmol of a solution of sodium methoxide in methanol (33.4 ml of 3.0 *M*) was added at 0°. The solution was maintained at 0°. In another 500-ml flask were placed 200 ml of absolute methanol and 200 mmol of sodium methoxide solution in methanol (66.8 ml, 3.0 *M*). The mixture was cooled to −78°, 200 mmol of bromine (10.4 ml) was added over 30 min, and the pale yellow colored solution was stirred for 15 min. To this solution was added through a double-ended needle under nitrogen pressure over 30 min the solution of *trans*-1-octenylboronic acid and sodium methoxide in methanol previously prepared. The reaction mixture was stirred for 30 min at −78° and then brought to room temperature. The product was extracted with 400 ml of *n*-pentane and 200 ml of water saturated with sodium chloride. The water layer was further extracted with *n*-pentane (200 ml × 2). The combined pentane extract was washed with 100 ml of water and dried over anhydrous magnesium sulfate. Following removal of the solvent, pure α-bromooctylaldehyde dimethyl acetal, bp 68° (0.15 mm), was obtained in 72% yield. The identification of the compound was carried out by a comparison of its ir, ^{1}H NMR, and mass spectra with those of an authentic sample.[4]