Peroxide. X. A Mild and General Synthesis of Peroxy Acids[1]

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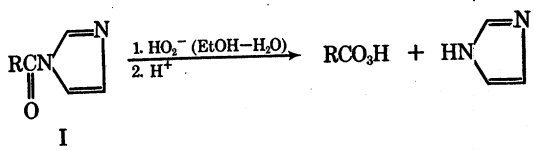
Peroxy acids are prepared in high yields by perhydrolysis of acyl diethyl phosphates in ethyl ether solution. The reaction is weakly catalyzed at low concentrations of methanesulfonic acid (MSA) but proceeds rapidly using equimolar proportions of MSA and the mixed anhydride. The acyl diethyl phosphate intermediates are prepared in ether solution by acylation of silver diethyl phosphate. The method is particularly useful for preparing methoxy-substituted and sterically hindered peroxy acids.

Many peroxy acids may be prepared by judicious choice of the methods and modifications currently available for their synthesis.[2,3] Some of the methods are comparatively superior to others for specific preparations, but each is limited in scope, yields, or preparative convenience. For example, the direct reaction between carboxylic acids and hydrogen peroxide in methanesulfonic acid solution is advantageous for preparing many peroxy acids in nearly quantitative yields, but the procedure fails in its application to the preparation of methoxy-substituted peroxybenzoic acids.[1] The monomethoxy derivatives, illustrated by peroxyanisic, are obtained in low yields (~35%) by alkaline perhydrolysis of either the acyl chloride[4] or the diacyl peroxide.[5]

Recently, Folli and Iarossi[6] have reported a new, general method for the preparation of peroxy acids, under mild conditions, that utilizes the imidazolides of carboxylic acids (I) (eq 1). The peroxy acids are ob-



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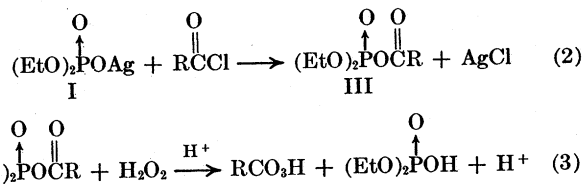
tained in yields averaging 50% by perhydrolysis of I in alkaline media. This method represents an improvement over former procedures for preparing methoxy-substituted peroxy acids and provides an effective route to the optically active and sterically hindered types.

In the course of our investigations of the kinetics of epoxidation,[7] several new peroxy acids were desired but were unobtainable by conventional methods. Since the synthetic method of Folli and Iarossi had not been published in the early stages of this work, we devised a new synthesis that appears to be general. The method takes advantage of the facility of acyl phosphates to hydrolyze under mild acid catalysis.[8]

The procedure entails the preparation of acyl diethyl phosphates (III) by acylation of silver diethyl phosphate (II) in ether solution (eq 2) and acid-catalyzed perhydrolysis of the mixed anhydride III to peroxy acid and diethyl hydrogen phosphate (eq 3). Although



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the silver salt is slightly soluble in ether, acylation proceeds instantaneously with the solid phase as well as in solution.

The conditions and yields for preparing various peroxy acids are recorded in Table I. The acid concentrations affecting the conversion of several mixed anhydrides to peroxy acids (Table II) were determined as a guide for formulating the preparative conditions listed in Table I. The method provides a conveniently useful and mild route to the preparations of methoxy-substituted and sterically hindered peroxy acids as well as others normally obtained with difficulty. The yields based on conversion of acid chloride average 75%.

TABLE I

PREPARATIVE CONDITIONS AND YIELDS OF PEROXY ACIDS

Acyl diethyl phosphate[a]	Mole ratio of H_2O_2:ADP:MSA[b]	Temp, °C	Time, hr	% peroxy acid[c]	Yield, %[d]
p-Methoxybenzoyl	10:2:1	10–15	1	89	82
	5:1:1	15	1	91	86
3,4,5-Trimethoxybenzoyl	5:1:1	15	1	88	63
2,4,6-Trimethylbenzoyl	5:1:0[e]	0–5	0.5	80	74
o-Nitrobenzoyl	5:1:2	25–30	1.5	74	74
p-Nitrobenzoyl	5:1:2	25–30	1.5	87	74
Stearoyl	5:1:1	25–30	1	92	74
Cinnamoyl	5:1:1	20	1.5	91	74
Pivaloyl	5:1:1	15	1	98	84

[a] Refer to Experimental Section for yields (based on acyl chlorides) and physical data of acyl diethyl phosphates. [b] ADP, acyl diethyl phosphate; MSA, methanesulfonic acid; H_2O_2, 98% concentration; reaction conducted in ethyl ether. [c] Based on iodometric analysis of crude product (see ref 15 for method used). [d] Yield of crude product based on acid chloride. [e] Reaction proceeds in the absence of MSA.

The disadvantage of the extra step for converting carboxylic acids to acyl chlorides is offset by the high yields of product. Folli and Iarossi[6] stressed the sensitivity of some types of carboxylic acids such as α or β optically active acids to the effects of strong acid environments as another disadvantage in the use of acyl chloride procedures. Examples of carboxylic acids

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(2) D. Swern in "Organic Peroxides," D. Swern, Ed., Wiley, New York, N. Y., 1970, pp 313–474.
(3) Reference 2, pp 475–516.
(4) M. Vilkas, *Bull. Soc. Chim. Fr.*, 1401 (1959).
(5) G. Braun, "Organic Syntheses," 2nd ed, Collect. Vol. I, Wiley, New York, N. Y., 1941, p 431.
(6) U. Folli and D. Iarossi, *Boll. Sci. Fac. Chim. Ind. Bologna*, **26**, 61 (1968).
(7) L. S. Silbert and D. A. Konen, Third Middle Atlantic Regional Meeting, American Chemical Society, Philadelphia, Pa., Feb 1968.
(8) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **153**, 571 (1944).

phosphate (9.14 g, 0.035 mol) in ethyl ether (50 ml): yield of oil product 6.05 g (85%); ir C=O at 1760, P=O at 1283, P—O—C at 1020 cm^{-1}.

Preparation of Peroxy Acids. Peroxyanisic Acid.—Hydrogen peroxide (3.4 g of 98% concentration, 0.10 mol) was added dropwise to a mixture of anisoyl diethyl phosphate (5.76 g, 0.02 mol) and methanesulfonic acid (0.96 g, 0.01 mol) in ethyl ether (10 ml) at 10–15°. After complete addition of hydrogen peroxide, the mixture was stirred for 90 min at room temperature. Ice-cold water was added (10 ml) and the peroxy acid was extracted with chloroform. The chloroform solution was water washed, briefly dried with anhydrous sodium sulfate, and evaporated to give peroxyanisic acid (3.36 g, 87% peroxy acid content by iodometric analysis.[1,16] The product was purified by recrystallization from chloroform (8 ml/g of peroxy acid) at 0°, mp 87–88° (lit.[17] 85–86°).

Other Peroxy Acids.—The peroxy acids were prepared by the procedure described for peroxyanisic acid using the following quantities of reactants. The reaction conditions, yields, and peroxy acid content are recorded in Table I.

3,4,5-Trimethoxyperoxybenzoic Acid.—Methanesulfonic acid (0.96 g, 0.01 mol) and H_2O_2 (1.7 g, 0.05 mol) were added to 3,4,5-trimethoxybenzoyl diethyl phosphate (3.48 g, 0.01 mol) dissolved in ethyl ether (10 ml) at 15°. The product (2.03 g, 88% peroxy acid content) was recrystallized from chloroform–petroleum ether (2:1, 15 ml) at −20°, mp 84–85°.

2,4,6-Trimethylperoxybenzoic Acid.—Methanesulfonic acid was not required as a catalyst for this preparation. H_2O_2 (3.4 g, 0.10 mol) was added to 2,4,6-trimethylbenzoyl diethyl phosphate (6.0 g, 0.02 mol) in ether (3 ml) at 0–5° and the reaction was completed at 15°. The product solidified from solution in 20 min (3.5 g, 80% peroxy acid content) and was recrystallized from ethyl ether–petroleum ether (5:3, 16 ml) at −20°, mp 55.5–57°. (Note that this compound is sometimes difficult to isolate in pure form. A semisolid peroxy acid was obtained from one preparation that spontaneously decomposed to tar with evolution of heat. In the case of studies not requiring the solid peroxy acid, it may be preferable to use the dried chloroform solution directly.)

***p*-Nitroperoxybenzoic Acid.**—Methanesulfonic acid (0.67 g, 0.007 mol) and H_2O_2 (0.30 g, 0.075 mol) were added to a solution of *p*-nitrobenzoyl diethyl phosphate (1.0 g, 0.0035 mol) in ethyl ether (2 ml) at 25–30°. The product (0.85 g, 87% peroxy acid content) was recrystallized from chloroform (30 ml) at 0°, mp 138–139° (lit.[1] mp 138° dec).

(16) (a) D. H. Wheeler, *Oil Soap*, **9**, 89 (1932); (b) D. Swern, *Org. React.*, **7**, 392 (1953).

(17) C. G. Overberger and R. W. Cummins, *J. Amer. Chem. Soc.*, **75**, 4250 (1953).

***o*-Nitroperoxybenzoic Acid.**—Methanesulfonic acid (1.96 g, 0.02 mol) and H_2O_2 (1.70 g, 0.05 mol) were added to a solution of *o*-nitrobenzoyl diethyl phosphate (3.03 g, 0.01 mol) in ethyl ether (5 ml) at 25–30°. The product (1.5 g, 74% peroxy acid content) was recrystallized from chloroform–petroleum ether (1:1, 40 ml/g) at 0°, mp 97–98° (lit.[1] mp 95–96°).

Peroxystearic Acid.—Methanesulfonic acid (0.98 g, 0.01 mol) and H_2O_2 (1.7 g, 0.05 mol) were added to a solution of stearoyl diethyl phosphate (4.21 g, 0.01 mol) in ethyl ether (15 ml) at 20° and the reaction was completed at 25–30°. The product (2.98 g, 92% peroxy acid content) was recrystallized from petroleum ether (20 ml/g) at 0°, mp 66–67° (lit.[1] mp 65°).

Peroxycinnamic Acid.—Methanesulfonic acid (0.96 g, 0.01 mol) and H_2O_2 (1.70 g, 0.05 mol) were added to a solution of cinnamoyl diethyl phosphate (2.94 g, 0.01 mol) in ethyl ether (3 ml). The product (1.60 g, 91% peroxy acid content) was recrystallized from chloroform–petroleum ether (1:2, 30 ml/g) at −20°, mp 75–76.5°.

Peroxypivalic Acid.—Methanesulfonic acid (1.96 g, 0.02 mol) and H_2O_2 (3.40 g, 0.10 mol) were added to a solution of pivaloyl diethyl phosphate (5.76 g, 0.02 mol) in ethyl ether (5 ml). A slight modification for the isolation of this low molecular weight peroxy acid was preferred to the use of chloroform as extraction solvent by the addition of ice and saturated ammonium sulfate solution and several extractions with olefin-free petroleum ether. The combined extracts were washed twice with ammonium sulfate solution, dried over anhydrous sodium sulfate, filtered, and analyzed volumetrically. The oily product (2.42 g, 98%) was recovered by evaporation of solvent but was not further purified.

Registry No.—Silver diethyl phosphate, 29912-99-0; anisoyl diethyl phosphate, 29913-00-6; 3,4,5-trimethoxybenzoyl diethyl phosphate, 29913-01-7; 2,4,6-trimethylbenzoyl diethyl phosphate, 29936-58-1; *p*-nitrobenzoyl diethyl phosphate, 29913-02-8; *o*-nitrobenzoyl diethyl phosphate, 29913-03-9; stearoyl diethyl phosphate, 29843-36-5; cinnamoyl diethyl phosphate, 29920-14-7; pivaloyl diethyl phosphate, 7334-50-1; peroxyanisic acid, 29913-05-1; 3,4,5-trimethoxyperoxybenzoic acid, 29913-06-2; 2,4,6-trimethylperoxybenzoic acid, 19910-28-2; *p*-nitroperoxybenzoic acid, 943-39-5; *o*-nitroperoxybenzoic acid, 1711-41-7; peroxystearic acid, 5796-86-1; peroxycinnamic acid, 16667-07-5; peroxypivalic acid, 14909-78-5.

Table II

Variation in Conditions for Conversions of Acyl Diethyl Phosphates to Peroxy Acids[a,b]

Acyl in ADP[c]	H_2O_2 concn (of soln), %	MSA/ADP[c,d] mole ratio	Time, hr	Peroxy acid, % formed
p-Methoxybenzoyl	65	1	3	28
	65	2	4	46
	98	0.2	2.5	38
	98	0.5	0.5	56
	98	0.5	1	71
	98	0.5	2	80
	98	1	0.5	88
	98	1	1	91
	98	1	1.5	89
2,4,6-Trimethylbenzoyl	98	0[e]	0.5	22
	98	0[e]	1	47
	98	0[e]	1.5	60
	98	0[e]	2	64
p-Nitrobenzoyl	98	1	2	0
	98	2	2	~1
	98	2	2 (25°)	11

[a] Solutions (1 *M*) in ethyl ether. [b] Reactions at 15° except where indicated. [c] ADP, acyl diethy lphosphate; MSA, methanesulfonic acid. [d] H_2O_2:ADP, 5:1 (mole ratio). [e] Perhydrolysis in absence of MSA.

from this class were not examined in the present work, but their conversion to acyl chlorides with retention of optical purity may be expected in view of the recently improved gentle techniques for conducting acyl chloride synthesis using dimethylformamide catalysis at low temperatures[9] or in the neutral environment of the triphenylphosphine–carbon tetrachloride reaction.[10]

Although the limited data of Tables I and II are inadequate for a mechanistic interpretation of the acid-catalyzed perhydrolysis of acyl diethyl phosphates, they suggest rate effects by substituents in the benzoyl moiety similar to those reported for the related hydrolysis of acyl phosphates $RC(=O)P(\rightarrow O)(OH)_2$.[11] A comparison of the differences in preparative conditions and yields of peroxy acids obtained from *p*-methoxybenzoyl and *p*-nitrobenzoyl diethyl phosphates (Tables I and II) suggests that the perhydrolysis rate decreases as the electron-withdrawing effect of the ring substituent increases. The ease of perhydrolysis of 2,4,6-trimethylbenzoyl diethyl phosphate, in the absence of acid catalysis, indicates that reaction may proceed *via* an acylium ion intermediate, since the steric compression of the two ortho methyl groups and the electron donation of the para methyl group would disfavor a bimolecular reaction.[12]

Experimental Section

Materials.—Hydrogen peroxide (98 and 65% concentrations) was obtained from Food Machinery and Chemical Corp. *Olefin-free* petroleum ether (bp 30–40°) was obtained by sulfuric acid treatment and distillation.

Diethyl Phosphate.—The reagent was prepared by the method of Toy.[13] (Note that the presence of hydrogen chloride as an impurity in diethyl phosphorochloridate induces an uncontrollable exothermic reaction with formation of undesired products. This may be avoided by distilling diethyl phosphorochloridate before use.[14])

Silver Diethyl Phosphate.—The silver salt was prepared by reaction of diethyl phosphate (18.59 g, 0.12 mol) and silver carbonate (13.78 g, 0.05 mol) in ethyl ether (100 ml) at 25°. The stirred slurry was filtered after decantation from the more dense unreacted silver carbonate that settles to the bottom of the flask. The filtered silver salt was ether washed and dried *in vacuo* at 90°, yield 21.4 g (82%).

Anal. Calcd for $C_4H_{10}AgO_4P$: C, 18.41; H, 3.86; Ag, 41.34; P, 11.87. Found: C, 18.56; H, 3.97; Ag, 41.07; P, 11.96.

Preparation of Acyl Diethyl Phosphates.—The preparation described for anisoyl diethyl phosphate is typical of the class of acyl diethyl phosphates. Elemental analyses were obtained only on the solid mixed anhydrides which were easily purified by crystallization. For the peroxy acid preparations, the anhydrides were used as obtained without further purification.

Anisoyl Diethyl Phosphate.—Anisoyl chloride (8.50 g, 0.05 mol) was added dropwise to a stirred slurry of silver diethyl phosphate (19.6 g, 0.075 mol) in ethyl ether (100 ml). The ether solution was stirred for 1 hr at 25° and filtered to remove unreacted silver diethyl phosphate and silver chloride. Filtrates that appeared clouded by small amounts of suspended silver salts were easily clarified by filtration through a small quantity of Florisil. Evaporation gave a light yellow oil (13.5 g, 94% yield) having the appropriate ir absorptions for carbonyl at 1740 and broad phosphorus–oxygen peaks at 1260 and 1025 cm^{-1} [reported absorptions for organophosphorus compounds:[15] P=O (unbonded) at 1350–1250, P—O—C (aliphatic) at 1050–990 cm^{-1}]. The oil product was used without further purification.

Other Acyl Diethyl Phosphates.—The phosphate anhydrides listed in Table I were prepared as described for anisoyl diethyl phosphate using the following quantities of reactants and reaction conditions.

3,4,5-Trimethoxybenzoyl Diethyl Phosphate.—3,4,5-Trimethoxybenzoyl chloride (6.9 g, 0.03 mol) was added to silver diethyl phosphate (10.4 g, 0.04 mol) in ethyl ether (25 ml), yield 7.45 g (72%). The prouct was recrystallized from ethyl ether–petroleum ether (2:1, 10 ml) at −20°: mp 44–45°; ir C=O at 1740, P=O at 1270, P—O—C at 1025 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}O_8P$: C, 48.28; H, 6.03; P, 8.91. Found: C, 48.44; H, 5.90; P. 8.82.

2,4,6-Trimethylbenzoyl Diethyl Phosphate.—2,4,6-Trimethylbenzoyl chloride (5.49 g, 0.03 mol) was added to silver diethyl phosphate (13.1 g, 0.05 mol) in ethyl ether (100 ml): yield 8.44 g (93%); ir C=O at 1758, P=O at 1290, P—O—C at, 1028 cm^{-1}.

***p*-Nitrobenzoyl Diethyl Phosphate.**—*p*-Nitrobenzoyl chloride (1.82 g, 0.01 mol) dissolved in ethyl ether (10 ml) was added to silver diethyl phosphate (4.12 g, 0.015 mol) in ethyl ether (25 ml). The product (3.0 g, 85% yield) recrystallized from ethyl ether–petroleum ether (1:1, 8 ml/g) to give a light yellow solid: mp 47–48°, ir C=O at 1740, P=O at 1280, P—O—C at 1030 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}NO_7P$: C, 43.57; H, 4.65; N, 4.62; P, 10.21. Found: C, 43.83; H, 4.75; N, 4.41; P, 10.26.

***o*-Nitrobenzoyl Diethyl Phosphate.**—*o*-Nitrobenzoyl chloride (5.75 g, 0.03 mol) dissolved in ethyl ether (25 ml) was added to silver diethyl phosphate (13.05 g, 0.05 mol), in ethyl ether (75 ml). The product (8.52 g, 95%) was a light yellow oil: ir C=O at 1752, P=O at 1280, P—O—C at 1025 cm^{-1}.

Stearoyl Diethyl Phosphate.—Stearoyl chloride (9.01 g, 0.03 mol) was added to silver diethyl phosphate (12.05 g, 0.05 mol) in ethyl ether (50 ml). The product (13 g, 100%) was purified by recrystallization from ethyl ether (2 ml/g) (note that if moisture is present some insoluble symmetrical stearic anhydride is formed): mp 36–37°; ir C=O at 1775, P=O at 1285, P—O—C at 1033 cm^{-1}.

Anal. Calcd for $C_{22}H_{45}O_5P$: C, 62.83; H, 10.78; P, 7.36. Found: C, 62.80; H, 10.85; P, 7.15.

Cinnamoyl Diethyl Phosphate.—Cinnamoyl chloride (5.00 g, 0.03 mol) dissolved in ethyl ether (25 ml) was added to silver diethyl phosphate (7.83 g, 0.03 mol) in ethyl ether (50 ml): yield of oil product 7.12 g (81%); ir C=O at 1735, P=O at 1270, P—O—C at 1030, C=C (aromatic conjugation) at 1628, HC=CH (trans) at 975 cm^{-1}.

Pivaloyl Diethyl Phosphate.—Pivaloyl chloride (3.62 g, 0.03 mol) dissolved in ethyl ether (5 ml) was added to silver diethyl