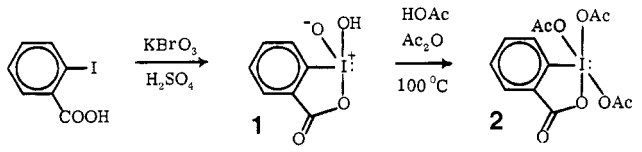
Readily Accessible 12-I-5[1] Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones

Summary: Periodinane[2] **2** is a mild, selective reagent for the oxidation of primary and secondary alcohols to aldehydes and ketones.

Sir: We report a readily prepared and relatively inexpensive 12-I-5[1] organoiodine compound, periodinane **2**, which is useful for the facile and efficient oxidation of primary alcohols to aldehydes and secondary alcohols to ketones. The reaction avoids some of the difficulties encountered in using other methods[3] for the oxidation of alcohols such as long reaction times,[3c] difficult workup procedures,[3d] or the need to use a large excess of the oxidizing agent.[3c]

Treatment of 2-iodobenzoic acid with $KBrO_3$ in H_2SO_4 gives the cyclic tautomer of 2-iodoxybenzoic acid, **1**, in 93%



yield.[4] A stirred slurry of **1** (25.0 g, 0.089 mol) in acetic anhydride (84.0 g, 0.83 mol) and acetic acid (70 mL) was heated to 100 °C. After 40 min the solid had dissolved. The solvent was removed under vacuum at room temperature until a thick slurry remained. Filtering the slurry in an inert atmosphere and washing with 180 mL of ether gave **2**[5,6] (35.1 g, 0.083 mol, 93%) in 87% overall yield from the iodobenzoic acid. Periodinane **2** has an indefinite shelf life in a sealed container. Long-term exposure to atmospheric moisture results in hydrolysis, but it can be used as an oxidizing agent in synthesis without using inert-atmosphere techniques if a slightly larger excess (e.g., 30%) of the reagent is employed, without lowering the yield of the reaction.

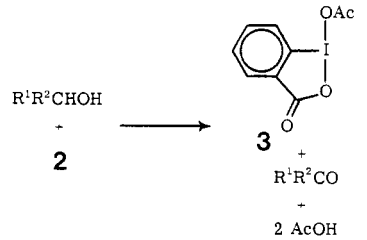
Table I. Oxidations of Alcohols to Aldehydes or Ketones with **2** in CH_2Cl_2 at 25 °C

alcohol	equiv of 2[d] (time, h)	added acid or base (concn, M)	yield, %
cyclohexanol	1.05 (0.5)	CF_3COOH (0.17)	90[a]
n-octanol	1.05 (0.5)	CF_3COOH (0.17)	83[a]
n-octanol	1.05 (1.0)	CF_3COOH (5.1×10^{-3})	94[a]
cyclooctanol	1.05 (1.0)	CF_3COOH (5.1×10^{-3})	99[a]
cyclooctanol	1.05 (1.0)	CH_3COOH (4.7×10^{-2})	84[b]
n-octanol	1.05 (1.0)	CH_3COOH (0.017)	93[a]
$PhCH_2OH$	1.05 (1.0)		91[a]
2,5-dimethoxybenzyl alcohol	1.10 (1.0)		94[b]
3,4,5-trimethoxybenzyl alcohol	1.10 (0.3)		94[b]
3,4,5-trimethoxybenzyl alcohol	1.10 (0.3)		90[b,c]
n-octanol	1.05 (1.0)	C_6H_5N (0.34)	86[a]

[a] Isolated yield of the 2,4-dinitrophenylhydrazone of the carbonyl product. Melting points for all derivatives agreed with literature values. [b] Isolated yield of purified product. NMR data and melting points were consistent with literature values. [c] Sodium thiosulfate workup. [d] Relative to alcohol, the initial concentration of **2** was approximately 0.16 M in each experiment.

Periodinane **2** is sparingly soluble in hexane or ether but is very soluble in chloroform, methylene chloride, or acetonitrile. A solution of **2** in one of these solvents rapidly oxidizes 1 equiv or less of a primary or secondary alcohol at room temperature to the corresponding aldehyde or ketone. No evidence for further oxidation of either product is seen under the conditions employed.

In a typical experiment, a solution of 3,4,5-trimethoxybenzyl alcohol (0.44 g, 2.23 mmol) in methylene chloride (8 mL) was added to a solution of **2** (1.05 g, 2.47 mmol) in methylene chloride (10 mL) with stirring. After 20 min the homogenous reaction mixture was diluted with 50 mL of ether, and the resulting suspension of iodinane **3** was



added to 20 mL of 1.3 M NaOH to hydrolyze **3** to the water-soluble 2-iodosobenzoate. After the mixture was stirred for 10 min, the ether layer was extracted with 20 mL of 1.3 M NaOH and with 25 mL of water. Removal of ether and Kugelrohr distillation of the remaining oily solid at 150 °C (0.2 mm) gave 3,4,5-trimethoxybenzaldehyde: 0.41 g (2.10 mmol, 94%); mp 71–73 °C (lit. mp 74–75 °C).[7] Table I lists yields of isolated products from several other oxidations. Yields determined by ^1H NMR spectroscopy were 100% in every case.

(1) The *N-X-L* designation, for a compound in which *N* valence shell electrons are formally involved in binding *L* ligands to the central atom X, was described earlier: Perkins, C. W.; Martin, J. C.; Arduengo, A. J.; Lau, W.; Alegria, A.; Kochi, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 7753.

(2) Organic derivatives of pentacoordinate iodine(V) are termed periodinanes. Amey, R. L.; Martin, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 300. Amey, R. L.; Martin, J. C. *Ibid.* **1979**, *101*, 5294.

(3) (a) House, H. O. "Modern Synthetic Reactions", 2nd ed; W. A. Benjamin: New York, 1972; p 257 and references therein. (b) Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030. (c) Guziec, F. S., Jr.; Luzzio, F. A. *Ibid.* **1982**, *47*, 1787. (d) Corey, E. J.; Suggs, W. J. *Tetrahedron Lett.* **1975**, 2647. (e) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. (f) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (g) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399. (h) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1975**, *97*, 5927. (i) Barton, D. H. R.; Godfrey, C. R. A.; Morzycki, W. J.; Motherwell, W. B.; Stobie, A. *Tetrahedron Lett.* **1982**, *23*, 957. (j) Moffitt, J. G. "Organic Synthesis"; Baumgarten, H. E., Ed.; Wiley: New York, 1973; Collect. Vol. V, p 242.

(4) We use a modification of the method of: Greenbaum, F. R. *Am. J. Pharm.* **1936**, *108*, 17. Potassium bromate (76.0 g, 0.45 mol) was added over a 0.5-h period to a vigorously stirred mixture of 2-iodobenzoic acid (85.2 g, 0.34 mol) and 730 mL of 0.73 M H_2SO_4. During the addition the reaction mixture was kept below 55 °C. The mixture was warmed to 65 °C and stirred for 3.6 h. Cooling to 0 °C, filtering, and washing with 1000 mL of water and two 50-mL portions of ethanol gave **1** (89.1 g, 0.32 mol, 93%).

(5) Mp 124–126 °C, dec; ^1H NMR δ 2.01 (s, 6, H on equivalent acetyl methyls), 2.27 (S, 3, unique $CH_3C{=}O$), 7.90 (unresolved d of d, 1) and 8.70 (unresolved d of d, 1) (Ar H at C-4 and C-5), 8.29 (d, 1 J = 8.5 Hz) and 8.31 (d, 1, J = 8.5 Hz) (Ar H at C-3 and C-6); IR (CH_2Cl_2) 1726.9 (s), 1707.5 cm^{-1} (s). Anal. ($C_{13}H_{13}IO_8$) C, H, I. Another structure for **2** in which the electron pair is opposite the endocyclic acyloxy ligand is consistent with the spectral data. The structure illustrated is preferred on the basis of structures reported for several aryltetrakis(acyloxy)periodinanes with perfluoroacyloxy ligands.[6]

(6) Aryltetrakis(acyloxy)periodinanes with perfluoroacyloxy ligands have been prepared. See: Yagupolskii, L. M.; Maletina, I. I.; Kondratenko, N. V.; Orda, V. V. *Synthesis* **1977**, 574. They are considerably less stable than the cyclic analogue, **2**, reported here. No other acetoxyperiodinanes have been reported.

(7) Semmler, F. W. *Chem. Ber.* **1908**, *41*, 1918.

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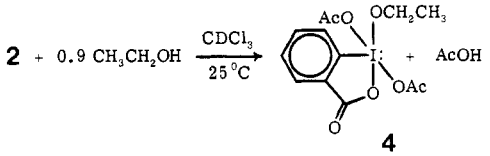
An alternative workup procedure[8] is useful for the synthesis of base-sensitive carbonyl compounds. Sodium thiosulfate reduces **3** to the water-soluble sodium salt of 2-iodobenzoic acid in sodium bicarbonate buffer in less than 10 min.

Either workup procedure is simpler and faster than that used for pyridinium chlorochromate,[3d] or other Cr(VI) reagents, which often produce tars which are purified with difficulty. Removal of the toxic and carcinogenic chromium species often requires time-consuming filtration procedures.[3c,d,g,h] The absence of such species in our procedure makes it particularly attractive for applications in medicinal chemistry. The use of dimethyl sulfoxide as an oxidizing agent[3f] also commonly requires much more complex workup procedures.

Recovery of the 2-iodo- or 2-iodosobenzoic acid for conversion to **2** simply involves acidification of the aqueous extracts and consistently results in a recovery greater than 95%.

If 0.9 equiv of ethanol is added to a solution of **2** in chloroform-*d*, a compound is formed whose ^{1}H NMR is consistent with structure **4**. The methylene quartet ap-



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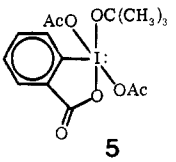
pears at 4.68 ppm and the methyl triplet at 1.42 ppm. The quartet for the methylene group in uncomplexed ethanol, at 3.68 ppm, is not seen. Two singlets, at 2.03 and 2.10 ppm, correspond to the acetate attached to iodine and acetic acid, respectively. Periodinane **4** gives acetaldehyde and **3** over a period of 1.5 h at 25 °C.

If 1 equiv of *tert*-butyl alcohol is added to a solution of **2** in chloroform-*d*, a compound whose ^{1}H NMR is consistent with structure **5**, an analogue of **4**, is formed. This



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compound is very stable in solution, but attempts to isolate it have not yet been successful. Both compounds **4** and **5** oxidize ethanol to acetaldehyde more rapidly than does **2**. If 1 equiv of ethanol is added to a solution of **4** or **5** at room temperature, its oxidation is almost instantaneous. The addition to **2** of as small an excess as 1.05 equiv, which would provide 0.05 equiv of alcohol beyond that required to form **4**, causes the reaction to go to completion in less than 20 min, much less time than is required for the oxidation of 0.9 equiv of ethanol. Addition of 1 equiv of a strong acid such as trifluoroacetic acid also catalyzes the reaction, giving almost instantaneous reaction. Added pyridine has little or no effect on the rate of the reaction. Further study of its mechanism is currently underway.

Periodinane **2** reacts much more rapidly with benzylic alcohols than with saturated alkanols. When 0.9 equiv of benzyl alcohol is added to a solution of **2** in chloroform-*d*, benzaldehyde is quantitatively formed in less than 20 min. A competitive oxidation using 1.00 equiv of **2** with 1.05 equiv each of ethanol and benzyl alcohol gives 78% benzaldehyde and 22% acetaldehyde. In similar competitive oxidations, periodinane **2** shows no selectivity between 2-propanol and ethanol. The basis for selectivity is not yet understood.

We have demonstrated that the readily accessible periodinane **2** is an effective reagent for the oxidation of alcohols to aldehydes or ketones with selectivity for benzyl alcohols. The reaction is catalyzed by acid or excess alcohol. The workup procedure is remarkably simple, and the conditions for reaction are very mild. By performing the reaction in the presence of pyridine and using the thiosulfate workup,[8] with sodium bicarbonate buffer, it is possible to maintain nearly neutral conditions throughout the entire reaction and isolation sequence.

Acknowledgment. This research was supported by a grant from the National Science Foundation (CHE 79-07-7905692). The NMR spectra were provided by the University of Illinois NSF Regional Instrumentation Facility (Grant CHE 79-16100) and mass spectra by facilities supported by grants from the National Institutes of Health (Grants CA 11388 and GM 16864).

Registry No. **1**, 61717-82-6; **2**, 87413-09-0; **3**, 1829-26-1; **4**, 87413-10-3; **5**, 87413-11-4; cyclohexanol, 108-93-0; *n*-octanol, 111-87-5; cyclooctanol, 696-71-9; benzyl alcohol, 100-51-6; 2,5-dimethoxybenzyl alcohol, 33524-31-1; 3,4,5-trimethoxybenzyl alcohol, 3840-31-1; cyclohexanone 2,4-dinitrophenylhydrazone, 1589-62-4; octanal 2,4-dinitrophenylhydrazone, 1726-77-8; cyclooctanone 2,4-dinitrophenylhydrazone, 1459-62-7; cyclooctanone, 502-49-8; benzaldehyde 2,4-dinitrophenylhydrazone, 1157-84-2; 2,5-dimethoxybenzaldehyde, 93-02-7; 3,4,5-trimethoxybenzaldehyde, 86-81-7; 2-iodobenzoic acid, 88-67-5; ethanol, 64-17-5; *tert*-butyl alcohol, 75-65-0.

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(8) The reaction mixture is diluted with ether and poured into saturated aqueous $NaHCO_3$ containing a sevenfold excess of $Na_2S_2O_3$. The mixture is stirred to dissolve the solid, and the layers are separated. The ether layer is extracted with saturated $NaHCO_3$ and with water. The ether is removed under vacuum and the product recrystallized or distilled.

Direct, Regiospecific 2-Lithiation of Pyridines and Pyridine 1-Oxides with in Situ Electrophilic Trapping

Summary: Efficient synthetic routes to 2-substituted pyridines and 2,6-disubstituted pyridine 1-oxides involving direct lithiation with the sterically hindered base lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in the presence of electrophiles that are compatible with the base, e.g., trimethylsilyl chloride (Me_3SiCl) and hexafluoroacetone (HFA), are described.

Sir: The directed ortholithiation of benzenes with heteroatom-centered substituents, by reaction with alkyllithiums, is an important and well-known synthetic reaction.[1] In contrast, the directed 2-lithiation of pyridines has not been found to be practical because of the greater ease with which alkyllithium derivatives add to the pyridine ring rather than act as a base to deprotonate the pyridine ring.[2]

(1) For a recent review, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(2) (a) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: Oxford, England, 1974; pp 112-116. (b) Francis, R. F.; Davis, W.; Wisener, J. T. *J. Org. Chem.* **1974**, *39*, 59.

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