

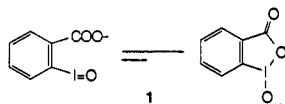
A Phosphorylated Iodosobenzoate: The Intermediate in the Iodosobenzoate Cleavage of a Reactive Phosphate

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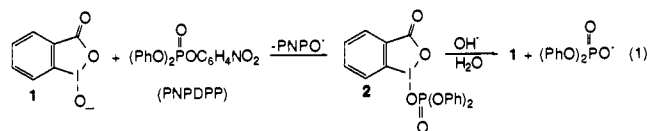
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During the past decade,¹ iodosobenzoic acid (IBA), **1**, has become the premier reagent for the rapid, catalytic cleavage of reactive esters and phosphates.² Its easy availability, utility in

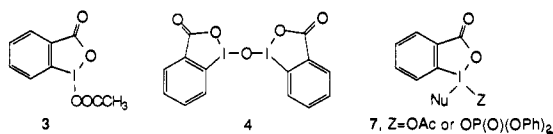


dilute aqueous micellar base, and demonstrated activity against several nerve agents³ have stimulated studies of IBA analogues,⁴ as well as varied modalities for IBA delivery, including micelles,^{1,2,5} liquid crystals,⁶ cationic latex dispersions,⁷ microemulsions,⁸ and IBA immobilized on solid supports.⁹

Despite intensive development, key mechanistic details of IBA's catalytic and hydrolytic function remain obscure. A likely scenario for the cleavage of a typical substrate, *p*-nitrophenyl diphenyl phosphate (PNPDPP), is shown in eq 1.^{5a} No evidence



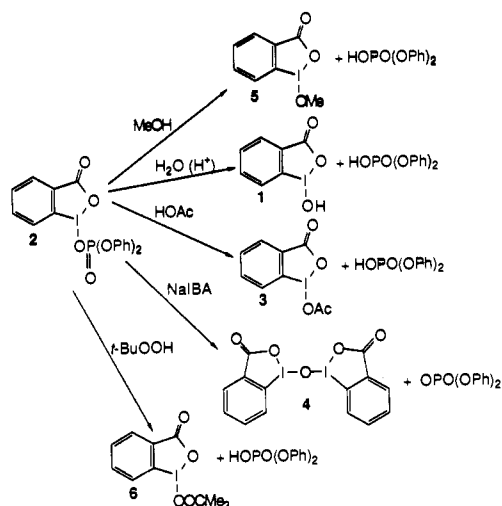
for the existence of the putative phosphorylated IBA intermediate, **2**, has yet been obtained. In the parallel cleavage of *p*-nitrophenyl acetate by IBA in DMSO, the formation and decay of the acetyl analogue, **3**, can be visualized by ¹H NMR.¹⁰ Although



acetoxyiodinane **3** can be directly prepared by the reaction of

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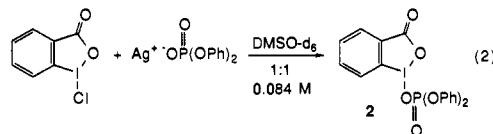
Scheme 1



IBA and acetic anhydride,^{10,11} previous attempts to prepare **2** have provided only **4**,¹¹ the anhydride of IBA^{5a} (see below).

Here, we describe the first successful generation of (phosphoryloxy)iodinane **2** and its ready derivatization by phosphate displacement at iodine with a variety of *O*-nucleophiles. The extraordinary ease of these reactions explains our inability to visualize **2** in previous attempts.^{5a}

Reaction of 1-chloro-1,2-benziodoxolin-3-one¹² with silver diphenyl phosphate,¹³ each 0.084 M in 1 mL of DMSO-*d*₆, afforded AgCl and a solution that revealed comparably intense ³¹P NMR singlets at δ -10.04 and -10.9 to -11.1;¹⁴ see eq 2. The



signal at $\sim\delta$ -11 is due to diphenyl phosphate-diphenyl phosphoric acid [HOP(O)(OPh)₂], as demonstrated by NMR spiking experiments,¹⁵ whereas the resonance at δ -10.04 is assigned to the desired iodosobenzoate-diphenyl phosphate ester, **2**, on the basis of chemical quenching experiments (see below).

Iodoso phosphate **2** is extremely sensitive to adventitious water, and diphenyl phosphate always accompanies its preparation; deliberate addition of traces of D₂O to DMSO-*d*₆ preparations of **2** increases diphenyl phosphoric acid (δ -10.9 to -11.1) at the expense of **2** (δ -10.04). In the absence of added water, **2** is reasonably stable in DMSO; the intensity of its NMR signal decreases about 12% in 30 min and about 67% in 5 h, so that reactions between **2** and added nucleophiles can be readily monitored. A series of such reactions appears in Scheme 1.

For each freshly prepared DMSO-*d*₆ solution of **2**, addition of excess nucleophile completely destroyed the phosphate ester (³¹P NMR), with the simultaneous formation of the appropriate product (**1**, **3**-**6**) and diphenyl phosphate (diphenyl phosphoric acid).¹⁶

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(14) ³¹P NMR spectra were determined at 81 MHz and are reported relative to an external standard of 85% H₃PO₄ in DMSO-*d*₆. Samples were prepared in a drybox. Unless otherwise noted, all chemical shifts refer to ³¹P.

(15) Pure silver diphenyl phosphate in DMSO-*d*₆ exhibits δ -9.22, while (PhO)₂P(O)OH is found at δ -11.22. Mixtures afford composition-dependent, averaged single signals between these limits.

(16) The corresponding ³¹P NMR signal appeared as a singlet between δ -10.57 and -11.29, depending on the presence of added water and cations, and the diphenyl phosphate/diphenyl phosphoric acid balance.

These reactions were complete within the requisite manipulation time of the NMR experiments (~ 3 min).

Reaction of **2** with excess MeOH gave diphenyl phosphoric acid ($\delta -11.20$) and the methoxyiodoxolinone **5**, identified by its ^1H NMR singlet at $\delta 4.16$ and by NMR spiking experiments with an authentic sample.^{10,11}

When **2** was reacted with either water or 5×10^{-3} N aqueous HCl, diphenyl phosphoric acid ($\delta -11.24$) and IBA (**1**) were formed. The latter was clearly identified by the distinctive ^1H NMR pattern of its aromatic protons. Note that the rapid destruction of **2** under acidic conditions agrees with our observation of fast turnover for a pyridinium iodosocarboxylate analogue of **2** at pH 5.4.¹⁷

The reaction of **2** with excess glacial HOAc gave diphenyl phosphoric acid ($\delta -11.20$) and 1-acetoxy-1,2-benziodoxolin-3-one (**3**), identified by its ^1H NMR methyl signal at $\delta 2.26$ ¹⁰ and by NMR spiking experiments with an authentic sample.^{10,11}

Reaction with excess NaIBA converted **2** to anhydride **4**, which was isolated by centrifugation and identified by FTIR comparison with an authentic sample.^{10,11} In addition, the formation of diphenyl phosphate ($\delta -10.57$) was observed.^{16,18}

Quenching the DMSO-*d*₆ solution of **2** with 20 μL of (Aldrich) 5.0–6.0 M *tert*-butyl hydroperoxide in 2,2,4-trimethylpentane (~ 20 –50% excess) gave diphenyl phosphoric acid ($\delta -11.19$) and the (*tert*-butyldioxy)iodinane **6**. The identity of **6** followed from its ^1H NMR *t*-Bu resonance ($\delta 1.28$) and TLC behavior ($R_f = 0.60$; SiO_2 , 2:1 $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$), both identical to those of an authentic sample.¹⁹

The ^{31}P NMR and chemical quenching results leave little doubt that the carrier of the $\delta -10.04$ resonance, formed as in eq 2, and rapidly destroyed by each of the reactions in Scheme 1, is indeed

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(18) Note that the ionization of phosphoric acid derivatives often produces downfield shifts in the ^{31}P NMR resonance; cf.: Gorenstein, D. G. *Phosphorus-31 NMR Principles and Applications*; Academic Press: New York, 1984; p 10 f.

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(phosphoryloxy)iodinane **2**.²⁰ Note that the reactions of Scheme 1 involve nucleophilic attack at iodine.²¹ Acyloxy and (phosphoryloxy)iodinanes such as **3** and **2** are subject to nucleophilic attack at I with the formation of hypervalent 12-I-4 intermediates,^{10,22} e.g., **7**, that subsequently lose acetate or diphenyl phosphate. The latter is the better leaving group, so that acetate **3** is less reactive and less rapidly destroyed by nucleophiles than phosphate **2**.²³ Therefore, **3** builds up and can be observed when IBA cleaves *p*-nitrophenyl acetate in DMSO.¹⁰

However, when NaIBA is reacted with PNPDP under similar conditions, we find only sodium diphenyl phosphate ($\delta -10.54$) and iodoso anhydride **4**; **2** is not observed after the manipulation time. Clearly, **2** cannot long survive in the presence of a nucleophile, in this case, IBA. IBA destroys **2** more rapidly than it cleaves PNPDP, so that the preparation of **2** can succeed only when the reagent combination is made as non-nucleophilic as possible, as in eq 2.

With the preparation of **2**, we are now in a position to study the generation of other highly reactive and labile iodinanes. These experiments are in progress.

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(20) Alkyl or aryl phosphates generally afford ^{31}P signals in the $\delta 0$ to -50 range; the chemical shifts are a sensitive function of the O–P–O bond angles. See Gorenstein, D. G., in ref 18.

(21) The conversion of **2** to **1** could involve hydrolysis at phosphorus, but this is unlikely, on the basis of the behavior of **3**¹⁰ and the other reactions in Scheme 1.

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(23) This implies that the decomposition of **7**, not its formation, is rate determining in IBA catalytic turnover.