Sodium Periodate (NaIO₄) in Organic Synthesis

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Key words sodium periodate (NaIO₄), oxidation, organic synthesis, catalysis

The periodate anion and sodium cation make up sodium periodate (CAS number: 7790-28-5) an inorganic salt. It can also be thought of as periodic acid’s sodium salt. Similar to numerous other periodates, it can be found in two distinct forms: sodium orthoperiodate (usually Na₂H₃IO₆, but occasionally the fully reacted salt Na₅IO₆) and sodium metaperiodate (formula NaIO₄). Both salts function well as oxidizers. Nitric acid can be used to dehydrate sodium hydrogen periodate, resulting in sodium metaperiodate. Eight oxygen atoms, spaced 2.54 Å and 2.60 Å apart, encircle the Na⁺ ions in sodium metaperiodate (NaIO₄), which forms tetragonal crystals (space group I₄₁/a) with somewhat deformed IO⁻₄ ions and average I–O bond lengths of 1.775 Å.²,³

The synthesis of many bioactive compounds and fine chemicals depends critically on the study of novel oxidative transformations for the creation of heteroatom–heteroatom and carbon–heteroatom bonds. In this context, the intriguing reagent NaIO₄ has garnered more interest since it makes it possible to produce these extraordinary oxidative changes that would be challenging to accomplish in any other way.⁴ As a result, NaIO₄ has been effectively investigated as a flexible oxidant for a range of fundamental chemical transformations, including the synthesis of bioactive natural compounds and intriguing oxidative transformations including C–H activation and oxidative functionalization of alkenes.⁵,⁶ With NaIO₄ serving as a flexible oxidant, this Spotlight article highlights recent advancements in the field (Table 1).

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<tr>
<th>(A) Oxidative dearomatization of N-Boc indoles:⁷</th>
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<tr>
<td>* ruthenium-catalyzed oxidative dearomatization * milder reaction conditions * excellent regioselectivity * good yields * scalable (up to gram scale)</td>
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\[
\text{R}^1 = \text{H, CH}_3 \quad \text{R} = \text{aliphatic, aromatic or cyclic}
\]

\[
\text{NaIO}_4 (1.5 \text{ equiv})
\]

10 examples, 48-92% yield

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<th>(B) Construction of C2-quaternary indolin-3-ones:⁸</th>
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\[
\text{R}^1 = \text{H, alkyl or Ar} \quad \text{R}^2 = \text{H or alkyl} \quad \text{R}^3 = \text{H, CH}_3, \text{Cl, etc.}
\]

\[
\text{NaIO}_4 (1.0 \text{ equiv})
\]

11 examples, 67-97% yield
(C) Diol cleavage: alternative protocol to ozonolysis
- oxidative cleavage of alkenes to aldehydes/ketones
- carbon–carbon bond cleavage in presence of other alkenes, oxidation sensitive moieties, and other functional groups
- mild conditions

(D) Synthesis of pyrimidines and pyridines:
- readily available starting materials
- transition-metal-free
- role of NaIO4 in selectivity
- ammonium salts as nitrogen sources
- selective multicomponent reaction

(E) Synthesis of indole-fused derivatives:
- good yields
- facile reaction conditions
- build multiple C–heteroatom bonds
- gram-scale synthesis
- convenient approach to hexacyclic-fused system that contained both indole and phenothiazine

(F) Oxidation of alcohols:
- reusability of MnP-POM catalyst (10 times)
- wide range of primary and secondary alcohols tolerance
- good selectivity

(G) Epoxidation of alkenes:
- reusable catalyst Ru(salophen)Cl supported on chitosan
- different alkenes such as linear, cyclic, and phenyl-substituted ones were employed

(H) Oxidative scission of olefins to aldehydes:
- selective oxidation of C=C bonds to aldehydes
- selective oxidation of C≡C bonds to α-diketones
- wide range of tolerable substrates, including highly functionalized sugar- and amino acid derived compounds
- this study underlines the general utility of the annulated αNHC ligand in organometallic catalysis and in particular oxidation chemistry

**Chemical Reactions**

**C1**

C1: Diol cleavage

Mn(ClO4)3 (0.01 mol%) PCA (0.5 mol%) H2O2 (1.5 mol%) R1/R2 = aliphatic/aromatic

**C2**

C2: Synthesis of pyrimidines and pyridines

NH4OAc (3 equiv) Fe(ClO4)3 (1.0 mol%) R1/R2 = aliphatic/aromatic

**C3**

C3: Synthesis of indole-fused derivatives

DMSO (3 equiv) PhCl, 130 °C, O2 Ar1 Ar2 + Ar1 Ar2

**C4**

C4: Oxidation of alcohols

MnP-POM catalyst (1.8 mol%) MnP-POM = Manganese porphyrin-polyoxometalate hybrid material

**C5**

C5: Epoxidation of alkenes

[Ru(salophen)Cl]@chitosan (5 mol%) R1/R1 = aliphatic, aromatic or cyclic

**C6**

C6: Oxidative scission of olefins to aldehydes

Ru catalyst (1 mol%) MeCN/EtOAc/H2O R = Ar, alkyl, Bn

**C7**

C7: Synthesis of pyrimidines and pyridines

NaIO4 (1 equiv) acetone–H2O (2:1) 8 examples up to 65% yield

**C8**

C8: Synthesis of indole-fused derivatives

NaIO4 (1 equiv) acetone–H2O (2:1) 8 examples up to 65% yield

**C9**

C9: Oxidation of alcohols

NaIO4 (2 equiv) DMSO (4 equiv) 35 examples, 36-83% yield

**C10**

C10: Epoxidation of alkenes

[Ru(salophen)Cl]@chitosan (5 mol%) 7 examples, up to 73% yield

**C11**

C11: Oxidative scission of olefins to aldehydes

NaIO4 (1 equiv) MeCN/EtOAc/H2O 24 examples, 45-100% yield

**C12**

C12: Synthesis of pyrimidines and pyridines

NaIO4 (1 equiv) acetone–H2O (2:1) 8 examples up to 65% yield

**C13**

C13: Synthesis of indole-fused derivatives

NaIO4 (1 equiv) acetone–H2O (2:1) 8 examples up to 65% yield
<table>
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<tr>
<th>(I) Oxidation of iodomethyl group:15</th>
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<tr>
<td>* do not lead towards overoxidation</td>
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<tr>
<td>* show good recyclability</td>
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<th>(J) Oxidation of iodomethyl group:15</th>
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<th>(K) Cleavage of an unnatural amino acid:16,17</th>
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<tr>
<td>* site-selective installation of an α-oxo aldehyde into proteins</td>
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<td>* shorter reaction times</td>
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<th>(L) Diol cleavage:18</th>
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<tr>
<td>* no racemization occurred</td>
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<td>* mild reaction conditions</td>
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<td>* optically pure compound is formed</td>
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<th>(M) Selective amine oxidation:20</th>
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<tr>
<td>* no overoxidation</td>
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<tr>
<td>* metal-free protocol</td>
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<tr>
<td>* oxidation of amines in aqueous–organic medium</td>
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<td>* unsymmetrical secondary amines underwent selective oxidation only at the benzylic position</td>
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<th>(N) Regioselective 1,2-difunctionalization of olefins:21</th>
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<tr>
<td>* molecular-iodine-free</td>
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<tr>
<td>* fast reaction</td>
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<td>* high yields</td>
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<td>* use of inexpensive reagents</td>
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<td>* broad applicability of nucleophiles</td>
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<td>* applicable for gram-scale synthesis</td>
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<th>(O) Synthesis of enantiomeric α-substituted hydroxy acids:22</th>
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<tr>
<td>* polysters with absolute atomic precision</td>
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<tr>
<td>* building blocks for the preparation of polysters with controlled molecular weights</td>
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Zhou et al. reported a highly selective oxidative dearomatization of \( \text{N-Boc} \) indoles using ruthenium as a catalyst, resulting in the production of indolin-3-ones. Moderate to high isolated yields (48–92%) were obtained for indoles with various substituents at the 2- and/or 5-position (Table 1, A).\(^7\) However, due to the decreased electron density, the 2-\( \text{H} \) indoles were nonreactive under ideal circumstances, and nearly all of the substrate was recovered. Notably, the ideal circumstances are unsuitable for the oxidative dearomatization of \( \text{N-acetyl} \) and \( \text{NH-indoles} \). Furthermore, Zhou et al. created indolin-3-ones with a C2-quaternary functionality by ruthenium-catalyzed oxidative dearomatization of 2-alkyl- or 2-aryl-substituted indoles (Table 1, B).\(^8\) According to their findings, substrates with 2-aryl or 2-methyl groups react in the best circumstances; nevertheless, when a 2-\( \text{H} \)-indole was used as the substrate, no target product was found. Moreover, \( \text{N-methyl} \) and \( \text{N-ethyl} \) indoles may also be oxidized at the optimized circumstances. They added that because of the low selectivity of the C–C bond formation reaction, the catalytic system was not suitable for a cross-reaction between two distinct indoles, such as 2-methylindole and 2-phenylindole or 2-methylindole and indole. The breaking down of alkene double bonds to produce di(\text{carbonyl}) molecules, such as ketone and aldehyde, is a crucial process in synthetic organic chemistry, particularly in medicinal and total synthesis.\(^9a–g\) As a substitute for ozonolysis, Eisink and colleagues reported a one-pot multistep procedure for the oxidative cleavage of alkenes to aldehydes/ketones in ambient circumstances (Table 1, C).\(^9b–g\) The first stage is the epoxidation/cis-dihydroxylation of alkenes, which is extremely effective when manganese is present. When required, a Fe(III)-assisted ring opening of the epoxide to a 1,2-diol occurs after this step.\(^9b\) By treating the diol with sodium periodate, carbon–carbon bonds can be broken. Because of the mild conditions (r.t.) used in all three steps, the described procedure allows for carbon–carbon bond cleavage in the presence of other alkenes, oxidation-sensitive moieties, and other functional groups. This makes it a viable general alternative to ozonolysis, especially for use under flow or continuous batch conditions. If the epoxidation is done in acetone, simple ring opening to the diol with \( \text{Fe(ClO}_4\text{)}_3 \) proceeds relatively quickly (depending on substrate) and could be followed by cleavage with only one equiv of \( \text{NaIO}_4 \), with overall reaction times of less than 4 h. Alternatively, the C–C bond cleavage can be performed directly on the epoxide with between 2 equiv and 4 equiv of periodate. Deng and his team developed an effective transition-metal-free synthesis of pyrimidines and pyridines from easily accessible aromatic ketones, aldehydes, and amonium salts (Table 1, D).\(^10\) Ammonium salts were utilized as the nitrogen source in this technique, and the only non-toxic byproduct that was produced was water. The regulation of selectivity was significantly influenced by the catalytic quantity of \( \text{NaIO}_4 \), while in its absence, substituted pyridines predominated in formation. To synthesize structurally valuable indolo[3,2,1-\( \text{k} \)]pyrrolo[3,2,1-\( \text{k} \)]quinolizines, Deng and his group further devised a mild two-step synthesis approach (Table 1, E).\(^11\) This chemical system was compatible with a wide range of functional groups, yielding a fair diversity of indolo[3,2,1-\( \text{k} \)]pyrrolo[3,2,1-\( \text{k} \)]quinolizines. By achieving the cascade synthesis of numerous C–heteroatom bonds, the current methodology provides a straightforward method of accessing a hexacyclic-fused system that contains the two favored skeletons, phenothiazine and indole. Using \( \text{NaIO}_4 \), Araghi showed how it can be applied to the MnP-POM catalyst at oxidizing primary and secondary alcohols to carbonyl compounds (Table 1, F).\(^12\) A variety of primary and secondary alcohols might be easily oxidized by this hybrid catalyst due to its strong reactivity. It demonstrated the anticipated benefits of recycability and ease of handling for heterogeneous catalysts. [Ru(salophen)Cl\( \text{@chitosan} \)] was found by Ardkani et al. to be an effective catalyst for the epoxidation of alkenes with \( \text{NaIO}_4 \) (Table 1, G).\(^13\) The catalyst exhibited no substantial loss in catalytic activity and could be easily recovered through filtration and reused multiple times. Bera et al. stated that utilizing \( \text{NaIO}_4 \) as an oxidant, the Ru-NHC ligand was shown to be an efficient catalyst for selective C=C bond scission of olefins to aldehydes and alkyne C=C bond oxidation to \( \alpha \)-diketones in an aqueous/organic solvent mixture at room temperature (Table 1, H).\(^14\) It was found that other oxidants, like oxygen and hydroperoxides, were ineffectual. It was discovered that the developed procedure worked well for both internal and terminal alkenes. The catalyst demonstrated a discernible rise in activity when employed with highly functionalized sugar and amino acid substrates. Alkynes were also subjected to
smooth oxidation using 2.1 equiv of NaIO₄. An intermediate that is high-valent Ru-oxo species was suggested by selective aldehyde production. The catalyst exhibited a definite increase in activity when used with highly functionalized substrates made of sugars and amino acids. The appropriate aldehydes or ketones were obtained in 25–51% of the substrates containing iodomethyl groups, according to Faisal’s and group report. The substrates were treated with the oxidizing agent NaIO₄ in the presence of DMF at 150 °C for 60–180 min under an argon atmosphere (Table 1, I).¹⁵

Using SPANC ligation to confer avidin affinity or fluorescent functionality through the use of reactive probes bearing biotin or dansyl groups, Fascione and his research group demonstrated the rapid unmasking of the highly reactive aldehyde by using NaIO₄ oxidation within 4 min. They also demonstrated its usefulness in protein bioconjugation (Table 1, J).¹⁶ This work eliminated a significant barrier on the application of this chemistry by demonstrating that SPANC bioconjugations were not restricted to the N-terminus. Similarly, Dimasi reported for the first time the conjugation of an antimitic medication to an antibody after a serine residue designed at the light chain’s N-terminus underwent mild and selective NaIO₄ oxidation.¹⁷ Dhatrak et al.,¹⁸ reported that 1,2,5,6-di-O-cyclohexyldiene-O-mannitol is easily cleaved into two molar equivalents of aldehyde using either NaIO₄ adsorbed on silica gel in DCM or NaIO₄ in diethyl ether/water system with added tetrabutylammonium bromide as phase-transfer catalyst (Table 1, K).¹⁸ Two molar equivalents of optical purity 2,3-O-cyclohexyldiene-δ-glyceraldehyde were obtained as a result. Qin et al. reported a practical procedure for the solely regio- and stereoselective bromine atom installation on 2-arylvinylsulfonyl fluorides using lithium bromide (LiBr) as the bromine source. This resulted in (Z)-1-bromo-2-arylethenen1-sulfonyl fluorides (Z-BASF) with adaptable reactive handles (vinyl, sulfonyl fluoride, and bromide) in ≥88% yield (Table 1, L).¹⁹ In the meantime, Z-BASF molecules showed a range of reactivities during a succession of chemical changes. Galletti and his team created a brand-new metal-free procedure to encourage amine oxidation in an aqueous–organic media. The most effective and selective method for oxidizing variously substituted benzyl amines to the corresponding benzaldehydes without overoxidation was found to involve NaIO₄ and TEMPO as the catalyst (Table 1, M).²⁰ Unsymmetrical secondary amines were oxidized selectively at the benzylic position, resulting in a benzylic group that was easily recovered through oxidative deprotection. Ultimately, the effectiveness of the optimized oxidative approach was validated by applying it to several cyclic amines, including dihydroindole, tetrahydroquinoline, and tetrahydroisoquinoline. This method mostly produced the corresponding aromatic derivatives. In the first generalized regioselective 1,2-difunctionalization of olefins, Majee et al. revealed a novel use of oxidizing reagent, a mixture of NH₂OH·HCl and NaIO₄ (Table 1, N).²¹ It was a generic procedure that involved employing various reaction media to β-iodo-β'-hydroxy ethers, β-iodo ethers, β-iodohydrin, and β-iodo acetoxy compounds. The reactions consistently produced Markovnikov’s type addition products and were very regioselective. The approach could also be used for terminal acetalts that are easily accessed. Kim and colleagues documented the production of enantiomeric α-hydroxy acids (OHAs) using alkenes and terminal epoxides as precursors (Table 1, O).²² Through a two-step process that involved first producing an aldehyde by Lemieux–Johnson oxidation of the alkene with OsO₄, and then producing an alnic acid by Pinnick oxidation with NaClO₂ and NaH₂PO₄, the terminal alkene was converted into a carboxylic acid.²²b–d The salient features of these protocols are: polymers with absolute atomic precision and building blocks for the preparation of polymers with controlled molecular weights. Secondary amines like Bn–NH–CH₂R (R = H, Me) can be oxidized by RuO₄ (produced in situ from RuO₂ and NaIO₄ to produce complex reaction mixtures, however, amides are the major product. The most abundant compounds in the presence of cyanide were α-amino nitritiles. Florea and associates completed this task (Table 1, P).²³

Using a crucial oxidative dearomatization approach, Vosburg and his team synthesized the corresponding epoxy ketone from salicyl alcohol driven oxidation via NaIO₄/H₂O.²⁴ Because of its plentiful supply, renewable nature, superior mechanical qualities, and adjustable surface chemistry, cellulose is a perfect starting material for the creation of functional materials. Mendoza et al. carried out a one-shot TEMPO–periodate oxidation of native cellulose.²⁵ Song and colleagues reported on the preparation method of the aldehyde sodium alginate (ASA) hydrogel utilizing NaIO₄.²⁶ In their work, Ziegler-Borowska et al. used sodium periodate to oxidize potato and maize starches, producing dialdehyde starch (DAS) with varying amounts of aldehyde groups.²⁷ Bhagavat Singh and Ramesh reported a unique, easy-to-use, and successful graphite oxidation technique.²⁸ The novel synthesis process, which was easy to remove impurities from without producing harmful gases, might be called nonmetallic oxidation of graphite. Using periodiated modified nanocellulose, Kara and colleagues developed an effective approach for the removal of methylene blue dye from wastewater.²⁹ Tunable stability/degradation profiles and ideal biological conditions are essential for biomaterials based on peptide-coupled alginites. According to Christensen and colleagues, peptide substitution of alginites via the periodate oxidation reductive amination process significantly alters the structure and maybe the stability qualities of the modified residues.³⁰ Despite the widespread usage of polysaccharides in food, it is still difficult to precisely characterize and/or identify their structures using a single technique. Plant polysaccharides undergo periodic oxidation to produce oligosaccharides that are unique to
each polymer. The study of Schols et al. study showed that in order for structurally distinct polysaccharides to depolymerize into oligosaccharides, they need to undergo distinct periodate oxidation conditions.\textsuperscript{31} Luo and Liu devised a simple, one-step method to alter the hydrophobic polyvinylidene fluoride (PVDF) microfiltration membrane’s superhydrophilicity and underwater superoleophobicity characteristics. This was achieved by depositing a highly effective polydopamine (PDA) coating that was oxidized by sodium periodate in a slightly acidic (pH = 5.0) environment.\textsuperscript{32} Che et al. reported that under acidic and/or neutral aqueous conditions, CAN, NaIO\textsubscript{4}, Oxone, or a mononuclear iron(III) complex with a macrocyclic N4 diazapyridinophane ligand catalyzed the oxidation of water to oxygen.\textsuperscript{33} In order to measure the electronic ligand effects that correspond to the activity of these compounds in catalytic water oxidation using sodium periodate, Hintermair et al. reported on the solution-phase electrospray of seven half-sandwich iridium(III) complexes with different pyridine-alkoxide ligands.\textsuperscript{34}

It has been demonstrated that sodium periodate is a more useful, affordable, and selective reagent for a wide range of oxidation reactions under ambient conditions with a broad substrate scope. NaIO\textsubscript{4} is also expected to be an effective oxidant and have a major influence on numerous other organic oxidative transformations. A number of areas need more research and exploration, even with the exciting advancements made in the field of oxidative transformation using sodium periodate. Future studies in this area will be crucial to significantly broadening the usage of periodates as beneficial oxidants from an applications standpoint.

Conflict of Interest
The authors declare no conflict of interest.

References
(26) Li, H.; Sun, Y.; Li, Q.; Luo, Q.; Song, G. ACS Biomater. Sci. Eng. 2022, 8, 598.

