

Oxidative Transformations by Iodine(V)

Of the many iodine(V) complexes synthesized,¹⁻³ two, 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (Dess-Martin periodinane, DMP) and 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one 1-oxide (*o*-iodoxybenzoic acid, IBX) (Figure 1), have gained considerable popularity as mild and selective oxidants for the conversion of alcohols to aldehydes and ketones. Recently, the scope of reactivity of DMP and IBX has been expanded by Nicolaou and co-workers.⁴⁻⁷

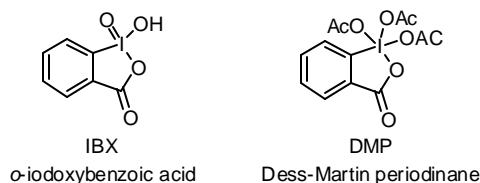
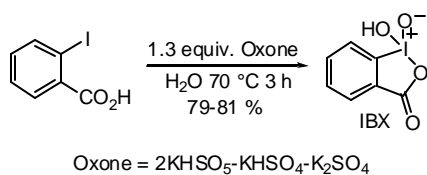


Figure 1

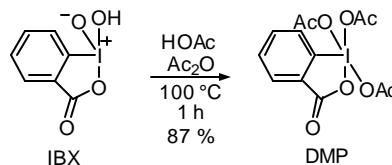
IBX was first reported in 1893;⁸ however, its ability to moderate alcohol oxidations was not reported until 1994,⁹ primarily due to the poor solubility of IBX. In 1994, Frigerio and Santagostino reported that using DMSO as the solvent is essential for the success of IBX in alcohol oxidations.⁹ Since 1893, the synthesis of IBX has



Scheme 1

evolved,¹⁰⁻¹² and today the most practical method involves the oxidation of 2-iodobenzoic acid by Oxone® (Scheme 1).¹³ In 1960, Bell and Morgan reported IR evidence of the cyclic structure of IBX¹⁴ which was confirmed by X-ray crystallography in 1981.¹⁵ Interestingly, the synthesis of IBX can lead to two different product morphologies.¹⁶ The macrocrystalline material is truly racemic and can be converted to the more reactive microcrystalline material. The microcrystalline powder is conglomerate in nature; each crystal is enantiomerically pure. A *warning*: IBX has been reported to decompose explosively above 190 °C and “under impact from a 534 g steel ball falling from a height of 1 meter.”¹⁷

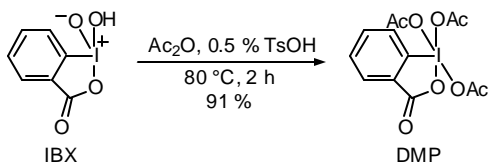
Prior to the use of IBX as a reagent for alcohol oxidation, its primary use was in the synthesis of Dess-Martin periodinane (Scheme 2).¹² The synthesis and utility of DMP was reported in 1983, and since that



Scheme 2

time DMP has gained widespread popularity with over 1,100 citations of the original

publication.¹² Ireland and Liu have reported an improved procedure for the synthesis of DMP using catalytic amounts of *p*-toluenesulfonic acid (Scheme 3).¹⁸



Scheme 3

The kinetics of alcohol oxidation by DMP and IBX have been studied. Both reactions

proceed by a fast pre-equilibrium alcohol complexation to the iodine(V) followed by rate-determining disproportionation of the iodic ester. For DMP, competition experiments^{12, 19} reveal that oxidation of benzyl alcohol is 5.9 times faster than oxidation of ethanol. However, alcohol oxidation by DMP does not appear to be affected significantly by sterics

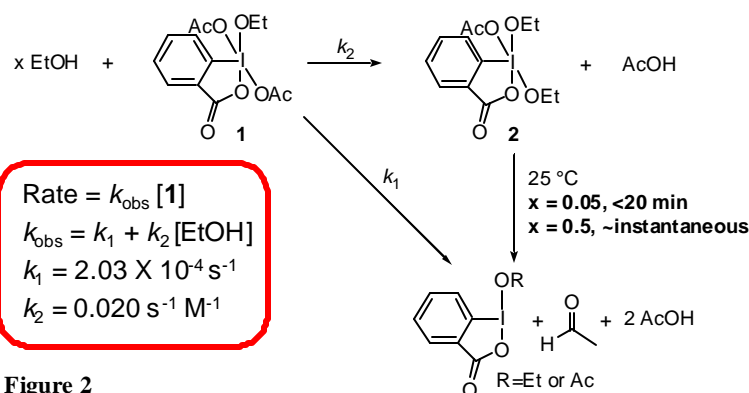
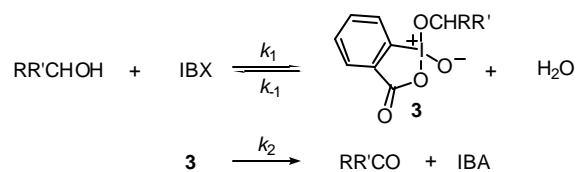


Figure 2

because ethanol and isopropanol are oxidized at approximately the same rates. Iodic ester disproportionation can be accelerated by the addition of excess alcohol or water (Figure 2).^{12, 19, 20}

For IBX moderated alcohol oxidation, a kinetic isotope effect of 6.3 (deuterium substitution gem to the hydroxy group) supports rate-determining disproportionation.^{21, 22}

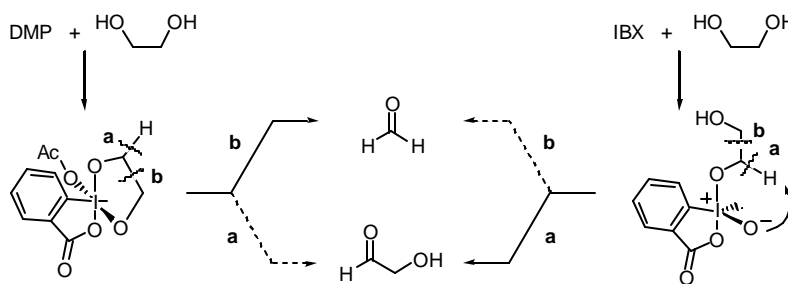
The proposed mechanism is shown in Scheme 4.²³ Santagostino and co-workers forced pseudo second-order conditions and used the pre-equilibrium hypothesis to solve for K_{eq} and k_2 .²³



Scheme 4

Although at first glance the mechanisms for DMP and IBX appear very similar, these reagents have demonstrated differences in reactivity, particularly with 1,2-diols (Figure 3).²³ DMP will cleave the glycol bond whereas IBX will oxidize the alcohol but leave the C-C bond intact. NMR studies have revealed that the difference is in coordination of the alcohol. DMP can coordinate an alcohol in either an axial or an

equatorial position. This ability allows a 1,2-diol to chelate and results in C-C bond



cleavage. IBX, conversely, can only coordinate an alcohol axially. Even large excesses of alcohol will not result in equatorial coordination. 1,2-diols can only bind to IBX in an

Figure 3

open-chain configuration, resulting in oxidation without glycol bond cleavage.²³

Alcohol oxidation by IBX and DMP are trusted procedures, so Nicolaou and co-

workers were surprised when they uncovered new modes of reactivity during their synthesis of the CP-molecules

phomoidride A and B (Figure 4).²⁴⁻²⁶

Anilides with pendant olefins form heterocycles,^{4, 6}

and once again, DMP and IBX demonstrate different reactivities

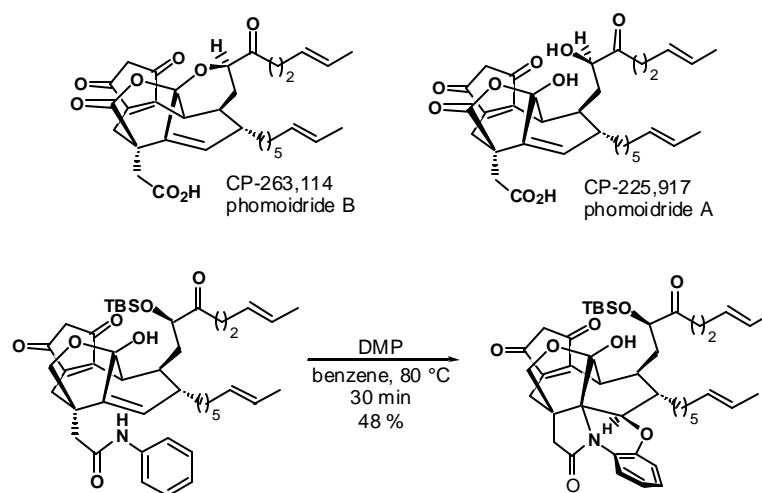


Figure 4

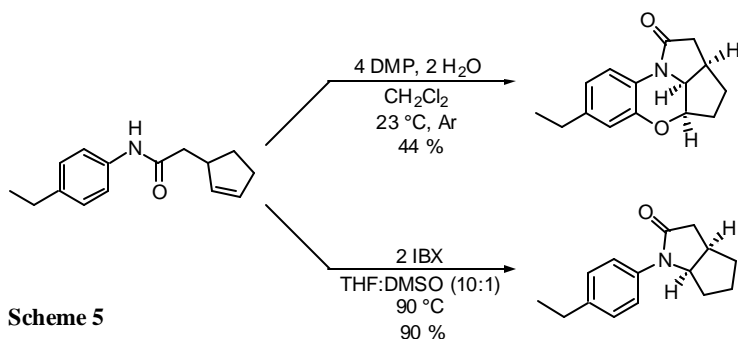
(Scheme 5). To gain a better understanding of this reactivity difference, mechanistic

studies were undertaken. It was discovered that the heterocyclization by DMP

requires water, implying a synergy between DMP and Ac-IBX (Figure 5).^{4, 27, 28}

Oxygen-18 labeling studies

have revealed that Ac-IBX is the source of the new oxygen atom in the heterocyclic



Scheme 5

product. An *o*-imidoquinone is a proven intermediate, and the reaction is not radical in

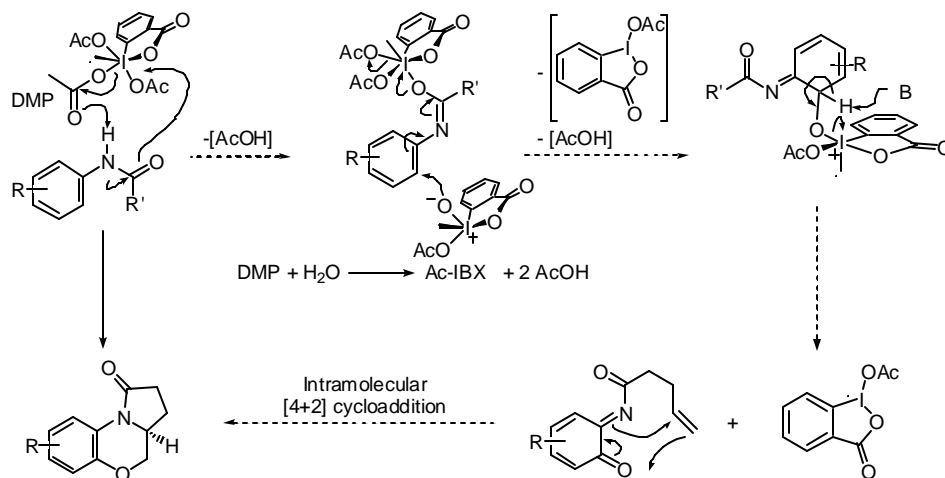


Figure 5

This *o*-imidoquinone intermediate was found to be useful as a diene for inter- and intramolecular hetero-Diels-Alder reactions,^{4, 27} as a dienophile for intramolecular Diels-Alder reactions,^{5, 29}

and as a substrate for oxidation of *p*-quinones (Figure 6).^{5, 30}

In contrast, heterocycle formation with IBX³¹ is proposed to be a single

electron transfer (SET) based process (Figure 7).⁶ Mechanistic studies^{6, 20} have shown that THF is required and appears to act as both a ligand on iodine(V) and as the H atom source. A Hammett correlation provides a ρ value of -1.4 , in the range consistent with a

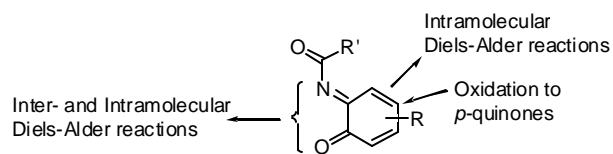


Figure 6

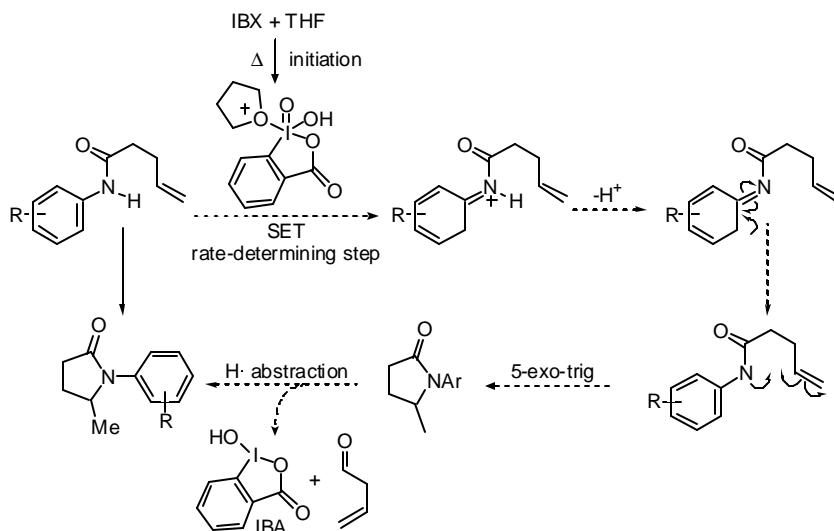
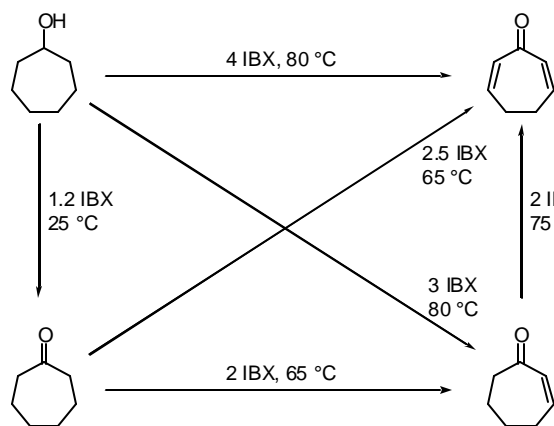


Figure 7

radical mechanism. Additional support for the radical nature of this transformation was provided by modifying the substrate to include a cyclopropane ring, which opens during

the reaction.^{6, 20} Nicolaou and co-workers demonstrated additional use of this heterocyclization reaction for the synthesis of amino sugars^{6, 32} by using *p*-methoxy phenyl as the aromatic group of the required anilide. The PMP group may be removed after the cyclization with ceric ammonium nitrate.

Unveiling the ability of IBX to act in SET based processes has prompted further studies of its use in additional reactions such as benzylic oxidation,^{7, 33} oxidation of



Scheme 6

occurs at elevated temperatures with THF and DMSO. Exploration of other oxide

ligands has led to the use of *N*-oxides, which both coordinate and lead to dehydrogenation activity at room temperature.³⁶ To date, the most promising ligand has been 4-methoxypyridine-*N*-oxide (MPO).

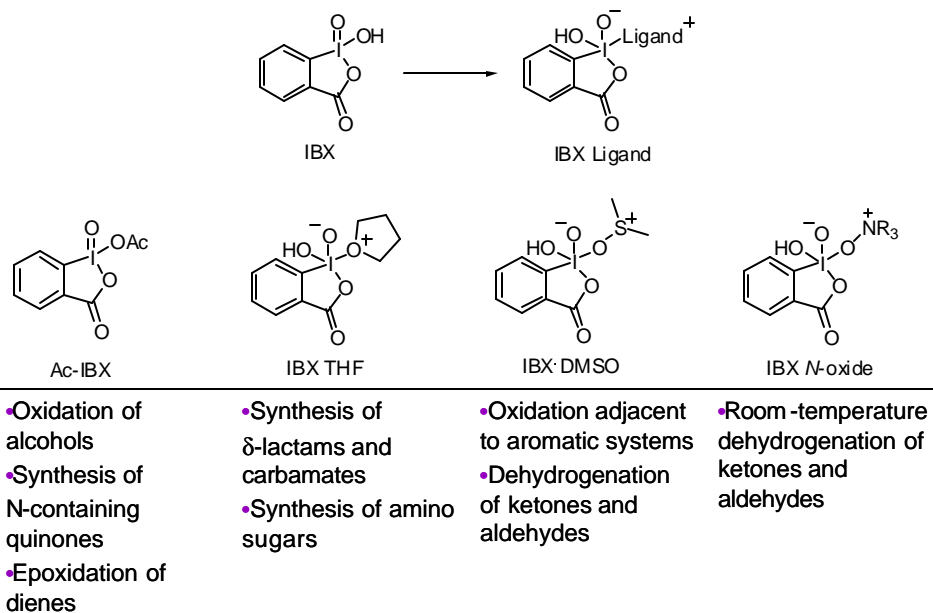


Figure 8

Upon MPO complexation to IBX, the oxidation of silyl-enol ethers proceeds in good to excellent yield at room temperature.³⁷ Discovering this ligand modulated reactivity has

led to questions regarding the other ligands on iodine(V) in the parent IBX molecule, namely the aromatic group. The SET based ketone dehydrogenation proceeds smoothly, even in the presence of unprotected primary alcohols, with reagents based on DMSO-coordinated iodic acid or iodine pentoxide.³⁸

Other recent developments in iodine(V) chemistry include the use of IBX on solid supports,³⁹⁻⁴¹ chiral iodine(V) complexes for the oxidation of thioethers,⁴² deoxygenation reactions by DMP and IBX,⁴³⁻⁴⁶ and a water soluble IBX derivative.^{47,48}

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