

Benziodoxole-Based Hypervalent Iodine Reagents in Organic Synthesis

Viktor V. Zhdankin*

Department of Chemistry, University of Minnesota Duluth, Duluth, Minnesota 55812, USA

Abstract: Five-membered hypervalent iodine heterocycles derived from benziodoxole and benziodazole oxide have recently emerged as reagents of choice for various synthetically useful oxidative transformations. In particular, IBX (2-iodoxybenzoic acid) and DMP (Dess-Martin periodinane) are widely used for the selective oxidation of primary and secondary alcohols and for a variety of other important oxidations. IBX-amides and IBX-esters are a new class of pentavalent iodine reagents with a pseudo-benziodoxole structure and a reactivity pattern similar to IBX.

Keywords: Hypervalent iodine, oxidation, benziodoxole, benziodazole, IBX, DMP.

1. INTRODUCTION

In the past decade, the organic chemistry of hypervalent iodine compounds has experienced an unprecedented, explosive development. Many reviews, some comprehensive, but most dealing with specific aspects of hypervalent organoiodine chemistry, have been published just in the last 5-6 years [1-31]. Most notable are the monograph by Varvoglis on the application of hypervalent iodine compounds in organic synthesis [1] and the volume of Topics in Current Chemistry on hypervalent iodine chemistry [2]. This surging interest in iodine compounds is mainly due to the very useful oxidizing properties of hypervalent iodine reagents, combined with their benign environmental character and commercial availability. Several areas of hypervalent iodine chemistry have recently attracted especially active interest and research activity. These areas include the use of iodosylbenzene in the transition metal catalyzed biomimetic oxygenations, catalytic imidations with iodonium imides, azidations with azidoiodanes, synthetic and mechanistic studies of alkynyl and alkenyl iodonium salts, and the synthetic applications of hypervalent iodine heterocycles derived from benziodoxoles and benziodazoles. Despite the widespread practical interest in the heterocyclic hypervalent iodine reagents, particularly, 2-iodoxybenzoic acid (IBX) and Dess-Martin periodinane (DMP), the chemistry of these compounds and their analogs was never systematically reviewed, but only briefly highlighted [25, 26].

The purpose of the present review is to summarize the recent literature data on synthetically useful heterocyclic hypervalent iodine reagents based on benziodoxole and on the related five-membered iodine(III) and iodine(V) heterocycles. Literature coverage is through the end of 2003.

2. FIVE-MEMBERED IODINE(III) HETEROCYCLES

The five-membered trivalent iodine heterocycles are represented by various derivatives of benziodoxole and

benziodazole (Fig. 1). The collective name "benziodoxoles" is commonly used for heterocycles (**1**) with iodine and oxygen incorporated in the five-membered ring and various substituents X attached to iodine [32]. The first derivatives of benziodoxole, 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one and 1-chloro-1,2-benziodoxol-3-(1*H*)-one, were prepared over 100 years ago by oxidation or chlorination of 2-iodobenzoic acid [33, 34]. In the mid-1980's, 1-hydroxybenziodoxoles have attracted a considerable interest and research activity mainly due to their excellent catalytic activity in the cleavage of toxic phosphates and reactive esters [4]. More recently, various new benziodoxole derivatives were synthesized and their usefulness as reagents for organic synthesis was demonstrated. In contrast to benziodoxoles, the analogous five-membered iodine-nitrogen heterocycles, benziodazoles (**2**), have received much less attention and, moreover, their structural assignment in some cases was not reliable. The most important and readily available derivative of benziodazole, acetoxybenziodazole (**2**, X = OAc, R = H), was first prepared in 1965 by the peracetic oxidation of 2-iodobenzamide [35].

X-ray molecular structures were reported for a number of benziodoxole derivatives [36-47]. In general, the five-membered ring in benziodoxole is highly distorted with almost linear alignment of the two electronegative ligands. The I-O bond length in benziodoxoles (**1**) (2R = O) varies in a wide range from 2.11 Å in carboxylates (**1**, X = *m*-ClC₆H₄CO₂) to 2.48 Å in the phenyl derivative (**1**, X = Ph), which indicates considerable changes in the ionic character of this bond. The endocyclic C-I-O bond angle is typically around 80°, which is a significant deviation from the expected angle of 90° for the normal T-shaped geometry of hypervalent iodine. The structural parameters of benziodazoles (**2**, X = OAc or Ph) in general are similar to those of benziodoxoles [48-50].

The distinctive feature of heterocyclic iodanes is a considerably higher stability than that of their acyclic analogs. This stabilization is usually explained by the bridging of the apical and the equatorial positions by a five-membered ring [36], and also by better overlap of the lone pair electrons on the iodine atom with the π -orbitals of the benzene ring [37]. The greater stability of benziodoxole enabled the preparation and isolation of otherwise unstable iodine(III) derivatives with I-OOR, I-N₃, I-CN and other

*Address correspondence to this author at the Department of Chemistry, University of Minnesota Duluth, Duluth, Minnesota 55812, USA; Tel: +218-726-6902; Fax: +218-726-7394; E-mail: vzhdanki@d.umn.edu

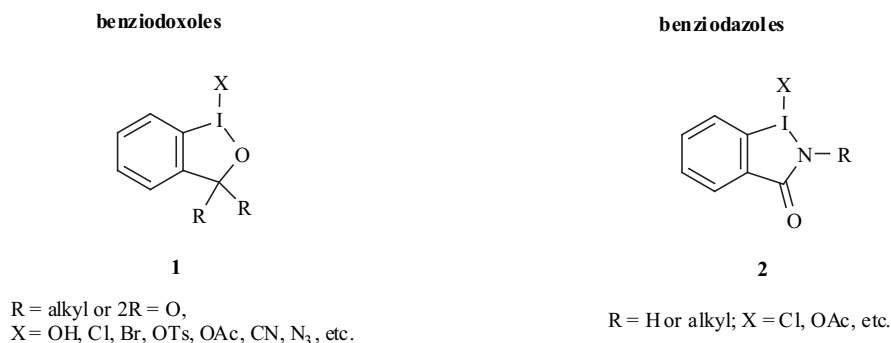


Fig. (1).

bonds. These various benziodoxole derivatives have found practical application as the reagents for oxidative functionalization of organic substrates.

2.1 Hydroxybenziodoxoles

The most important and best investigated representative of benziodoxoles is the commercially available 1-hydroxy-1,2-benziodoxole-3(1*H*)-one (**3**) - the cyclic tautomer of 2-iodosylbenzoic acid (**4**, R = H) (Fig. 2). Moss and coworkers [51] reported the results of a structural re-investigation of 4-alkyl-2-iodosylbenzoic acids, for which an open tautomeric form (**4**) was previously assigned by others. Contrary to the previous report [52], only the closed, iodoxolone form (**5**) of 4-alkyl-2-iodosobenzoic acid can be isolated; the previously assigned open (iodoso) form is actually 4-pentanoyl-2-iodobenzoic acid [51].

1-Hydroxy-1,2-benziodoxole-3(1*H*)-one (**3**) is commercially available or can be easily prepared by direct oxidation of 2-iodobenzoic acid or by basic hydrolysis of the respective iododichloride [53, 54]. In the last twenty years, hydroxybenziodoxoles have attracted considerable research interest due to their excellent catalytic activity in the

cleavage of toxic phosphates and reactive esters [4]. This activity is explained by a pronounced O-nucleophilicity of the benziodoxole anion (**6**) due to the α -effect. Spectral and kinetic mechanistic studies indicate that the highly unstable iodoxole derivatives, such as phosphate (**8**), are the reactive intermediates in the catalytic cleavage of phosphates, as shown for the catalytic hydrolysis of a typical substrate (**7**) (Fig. 3) [55-57]. To prove this mechanism, Moss and coworkers have generated phosphate (**8**) from 1-chloro-1,2-benziodoxole-3(1*H*)-one and silver diphenyl phosphate and investigated its NMR spectra and chemical reactions *in situ*. In particular, phosphate (**8**) in a DMSO solution is extremely sensitive to water and instantaneously reacts with methanol, water, acetic acid and other nucleophiles to afford the appropriate products of nucleophilic substitution.

Hydroxybenziodoxole (**3**) has found some practical application in organic synthesis as a mild oxidizing reagent. Ochiai and coworkers have found that tetrabutylammonium salt of benziodoxole (**10**) reacts with α,β -unsaturated carbonyl compounds (**9**) yielding *trans*-epoxides (**11**) with high stereoselectivity (Fig. 4). This reaction probably involves a nucleophilic attack of the benziodoxole anion on the electron-deficient double bond [58].

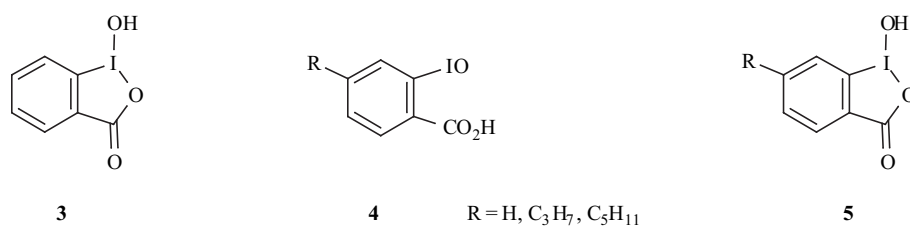


Fig. (2).

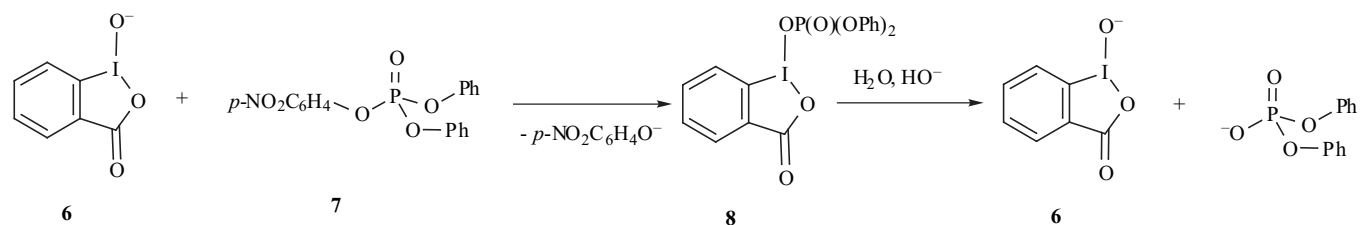


Fig. (3).

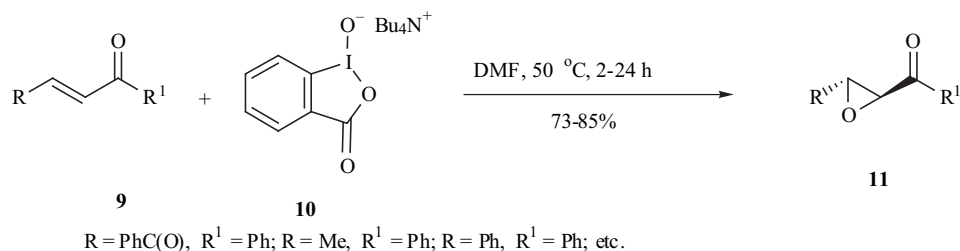


Fig. (4).

Hydroxybenziodoxole (**3**) has also found wide application as a starting compound for the preparation of various benziodoxole-based hypervalent iodine reagents by ligand exchange on iodine.

2.2 Sulfonate Derivatives of Benziodoxole

Sulfonate derivatives (**12-14**) and (**16-18**) can be conveniently prepared by a simple, one step procedure starting from hydroxybenziodoxoles (**3**) or (**15**) and the corresponding sulfonic acids or trimethylsilyltriflate (Fig. 5) [59, 60]. All sulfonates were isolated as moderately hygroscopic, but thermally stable, crystalline solids. The

most stable to moisture are tosylates (**14**) and (**18**). Mesylates and triflates are more hygroscopic and can be isolated only in the form of crystalline hydrates; however, for further reactions they can be conveniently used *in situ* [60].

Like the other iodine(III) derivatives of strong acids, sulfonates (**12-14**) and (**16-18**) are highly reactive toward unsaturated organic substrates and other carbon nucleophiles. For example, mesylate (**13**) reacts with cyanotrimethylsilane with the formation of the cyaniodonium salt (**19**) while a similar reaction of triflates (**12**) and (**18**) with trimethylsilylated alkynes followed by addition of pyridine selectively affords 1-alkynylbenziodoxoles (**20**) and (**21**) in a high preparative yield (Fig. 6) [59, 60].

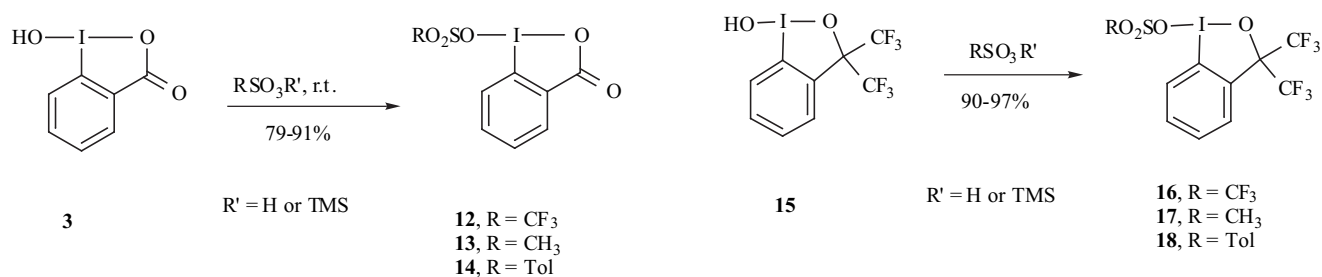


Fig. (5).

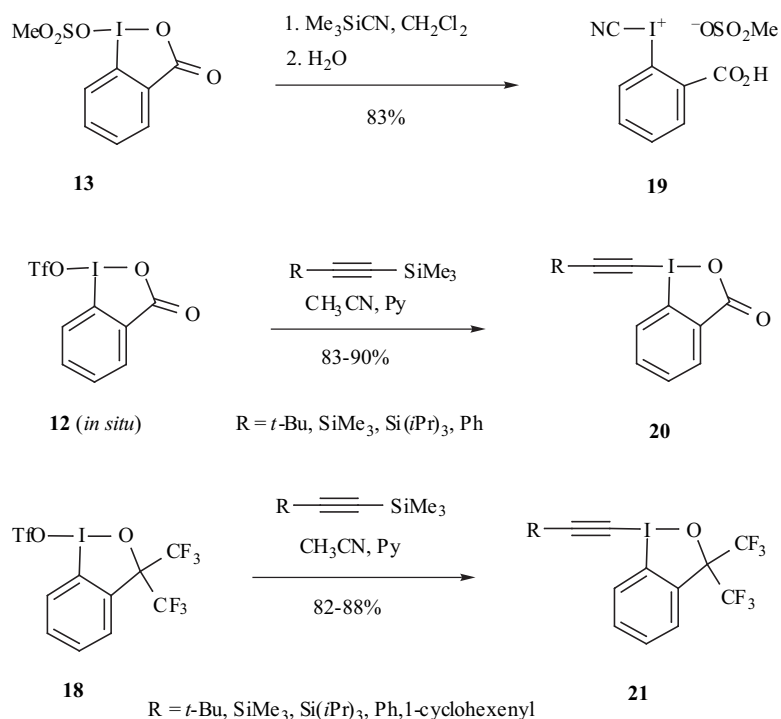
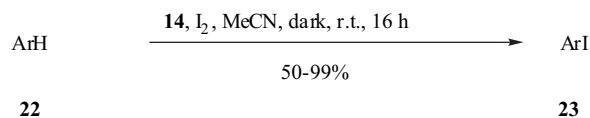


Fig. (6).

Muraki, Togo, and Yokoyama have demonstrated that tosyloxybenziodoxole **14** can be used as an effective reagent for the oxidative iodination of aromatic compounds [61, 62]. Treatment of various aromatic compounds **22** with reagent **14** and I₂ gives the corresponding iodinated compounds **23** in good yields (Fig. 7). Similarly, both chlorination and bromination proceed effectively. As compared with other trivalent iodine compounds, the tosylate **14** shows the best reactivity as a halogenation reagent.



ArH = 1,3,5-(MeO)₃C₆H₃, 1,3,5-(*i*-Pr)₃C₆H₃, 1,3,5-Me₃C₆H₃,
1-MeO-4-MeCO₂C₆H₄, 1-MeO-4-BrC₆H₄, 1,4-Me₂C₆H₄, 1,3-Me₂C₆H₄,
MeOC₆H₅, *t*-BuC₆H₅, AcOC₆H₅, naphthalene, 2,3-benzothiophene, etc.

Fig. (7).

Likewise, the reagent **14**/iodine system can be used for the iodotosyloxylation of alkynes **24** to give the addition products **25** in good yields (Fig. 8) [62]. These reactions presumably proceed *via* the intermediate formation of arenesulfonyl hypoiodites.

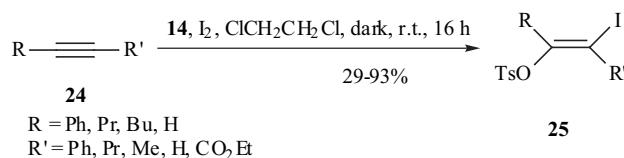


Fig. (8).

2.3 Alkylperoxybenziodoxoles

The greater stability of heterocyclic iodanes enables the isolation of otherwise unstable iodine(III) derivatives with I-OOR bonds. Ochiai and coworkers reported the preparation of 1-(*tert*-butylperoxy)benziodoxoles (**28**) and (**29**) by treatment of the appropriate benziodoxoles (**26**, **27**) with *tert*-butyl hydroperoxide in the presence of BF₃-etherate (Fig. 9) [63]. Peroxides (**28**) and (**29**) are stable, crystalline products which can be safely stored at room temperature for an indefinite period of time.

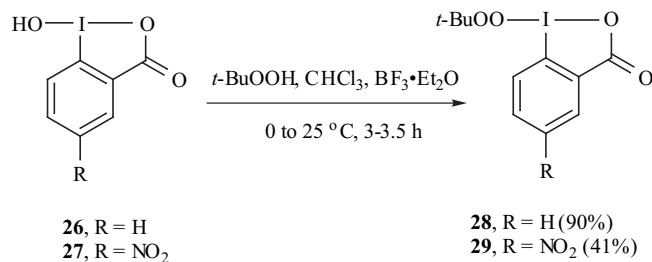


Fig. (9).

Dolenc and Plesnicar reported an alternative procedure for the preparation of 1-(*tert*-butylperoxy)benziodoxoles **31** from the corresponding chloriodanes **30** and *tert*-butyl hydroperoxide in the presence of potassium *tert*-butoxide in THF (Fig. 10) [64].

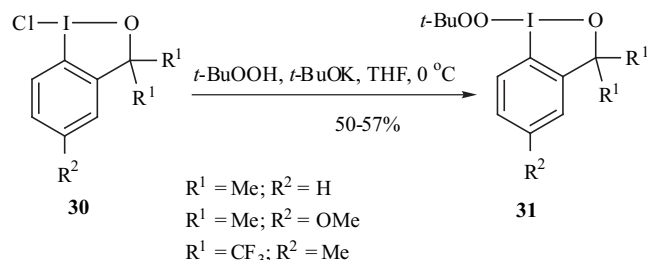


Fig. (10).

In a series of papers, Ochiai and coworkers have demonstrated that peroxyiodane **28** is a useful reagent acting as a strong oxidizer toward a variety of organic substrates, such as ethers, organic sulfides, amides, and phenols [63, 65-69].

Peroxyiodane (**28**) oxidizes various benzyl and allyl ethers (**32**, **34**) to the respective esters (**33**, **35**) under mild conditions in the presence of alkali metal carbonates (Fig. 11) [63]. Since this reaction is compatible with other protecting groups such as MOM, THP, TBDMS ethers, and acetoxy groups, and because esters are readily hydrolyzed under basic conditions, this new method provides a convenient and effective alternative to the usual reductive deprotection.

Under similar mild conditions, peroxyiodane (**28**) oxidatively cleaves cyclic acetals (**36**) to glycol monoesters (**37**) (Fig. 12) [65].

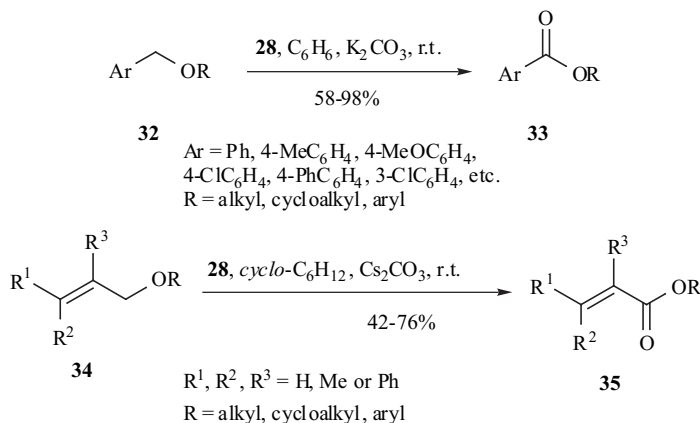


Fig. (11).

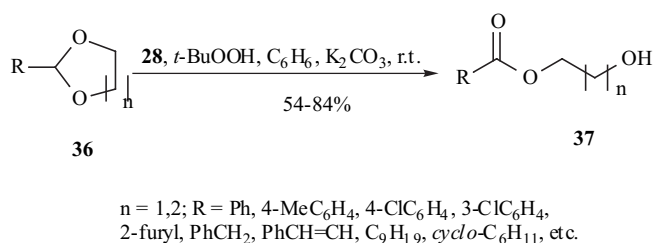


Fig. (12).

Sulfides (**38**) can be oxidized with peroxyiodane (**28**) under mild conditions to afford sulfoxides (**39**) in high yields (Fig. 13) [66]. A similar oxidation of dithioacetals (**40**) leads to the regeneration of the parent carbonyl function (Fig. 13) and thus can be useful as a method for selective deprotection [66].

Amines (**42**) are oxidized by peroxyiodane (**28**) at the α -methylene carbon yielding amides (**43**) as major products (Fig. 14) [67]. Under similar conditions, the oxidation of secondary amines affords the respective imines [68].

The oxidation of 4-alkylphenols (**44**) by peroxyiodane (**28**) in the presence of *tert*-butyl hydroperoxide affords

selectively 4-(*tert*-butylperoxy)-2,5-cyclohexadien-1-ones (**45**) in good yields (Fig. 15) [69].

2.4 Azidobenziodoxoles

Hypervalent iodine azides in general lack stability and are sensitive to moisture. Non-cyclic azidoiodanes, $\text{PhI}(\text{N}_3)\text{X}$ ($\text{X} = \text{OAc, Cl, OTMS, etc.}$) or $\text{PhI}(\text{N}_3)_2$, were proposed as reactive intermediates in azidonation reactions involving the combination of PhIO or $\text{PhI}(\text{OAc})_2$ with trimethylsilyl azide or NaN_3 [32]. Attempts to isolate these intermediates always resulted in their rapid decomposition at -25 to 0°C with the formation of iodobenzene and dinitrogen; however, low temperature spectroscopy and the subsequent chemical reactions *in situ* provided some experimental evidence toward the existence of these species. The incorporation of the hypervalent iodine into a five-membered heterocycle leads to a significant stabilization of azidoiodane. The first stable azidobenziodoxoles were prepared independently in our laboratory [70] and by Kita and coworkers [46]. In our work, azidobenziodoxoles (**47-49**) were synthesized in one step by the reaction of hydroxybenziodoxoles (**46**) with trimethylsilyl azide in acetonitrile (Fig. 16) [44, 70], while Kita and coworkers [46] used acetoxybenziodoxole as

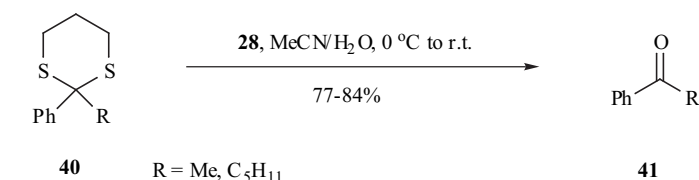
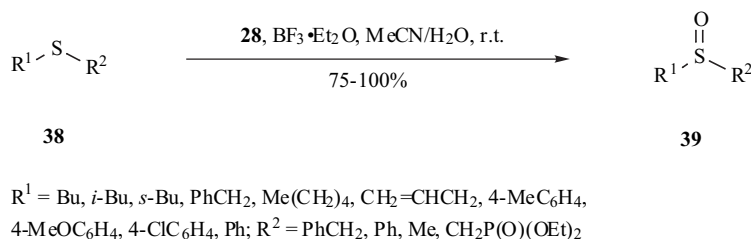


Fig. (13).

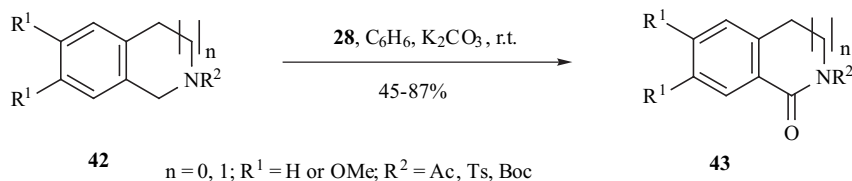


Fig. (14).

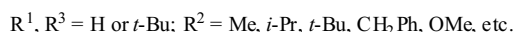
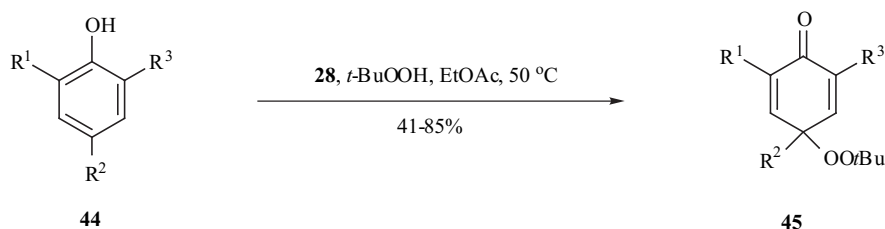


Fig. (15).

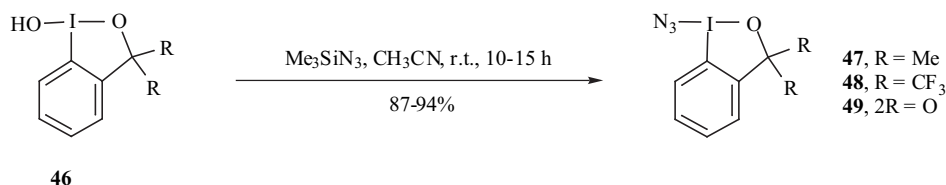


Fig. (16).

starting material for the preparation of azidobenziodoxole (49).

The structure of azidobenziodoxole (48) was unambiguously established by a single-crystal X-ray analysis. The structural data revealed the distorted T-shaped geometry, typical of hypervalent iodine, with an N-I-O bond angle of 169.5°. The lengths of the bonds to the iodine atom, I-N (2.18 Å), I-O (2.13 Å), and I-C (2.11 Å), all have similar values and generally are within the range of typical single covalent bonds in organic derivatives of polyvalent iodine [44].

Azidobenziodoxoles can be used as efficient azidating reagents toward various organic substrates (Fig. 17) [44, 70]. In a typical example, reagent (49) reacts with *N,N*-

dimethylanilines in dichloromethane at reflux in 30 min to afford the respective *N*-azidomethyl-*N*-methylanilines (50) in excellent yield. The main advantage of reagent (49) over the known, unstable PhIO/TMSN₃ reagent combination, is high thermal stability allowing its use at higher temperatures. We have found that azidobenziodoxoles (48) and (49) can even be used for direct azidation of hydrocarbons at high temperatures and in the presence of radical initiators (Fig. 17). Reagent (49) selectively reacts with isooctane upon reflux in 1,2-dichloroethane in the presence of catalytic amounts of benzoyl peroxide to afford tertiary azide (54) and 2-iodobenzoic acid as the only products. Under similar conditions, reactions of azidobenziodoxoles (48) or (49) with bicyclic and tricyclic hydrocarbons afford the respective alkyl azides (51-53) [44].

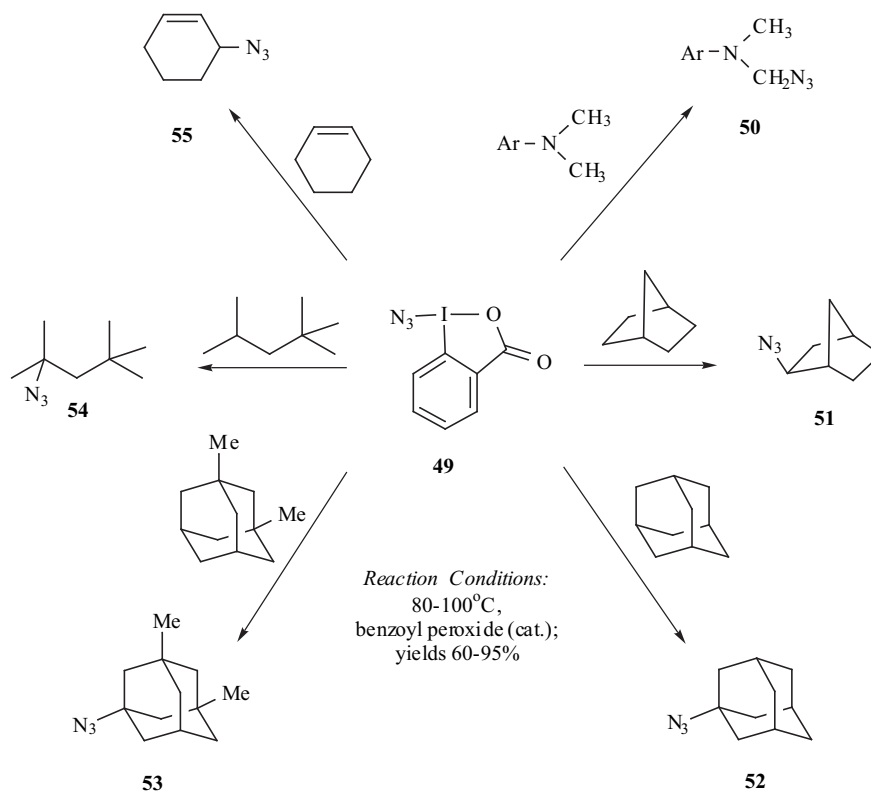


Fig. (17).

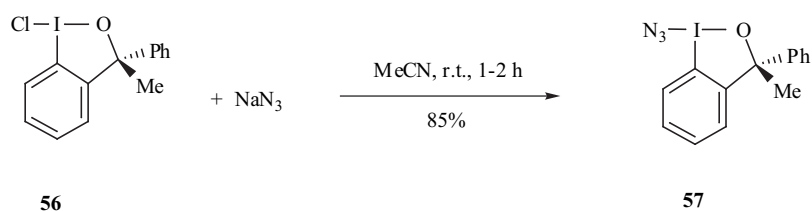


Fig. (18).

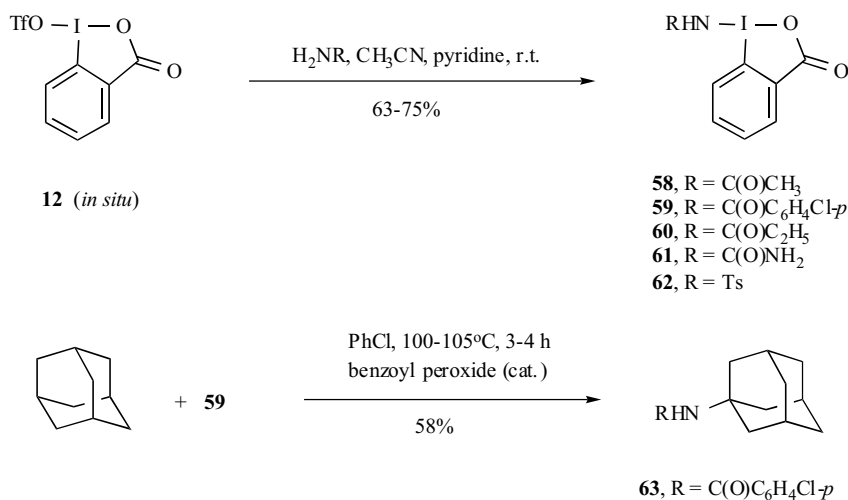


Fig. (19).

The mechanism for azidation of alkanes with reagent (**49**) clearly has a free-radical origin, which is consistent with the literature data on radical mechanism for azidations by the unstable azidoiodanes, $\text{PhI}(\text{N}_3)_2$ and $\text{PhI}(\text{N}_3)\text{OTMS}$.

Koser and Rabah reported the synthesis of optically active 1-azido-1,3-dihydro-3-methyl-3-phenyl-1,2-benziodoxole (**57**) (Fig. **18**) [71]. This homochiral azidobenziodoxole is a potentially useful reagent for asymmetric azidation reactions.

2.5 Amidobenziodoxoles

Amidobenziodoxoles (**58-62**) can be conveniently prepared in one step from the triflate (**12**) and the appropriate amide, RNH_2 (Fig. **19**) [72]. All five adducts (**58-62**) were isolated as thermally stable, white, non-hygroscopic, microcrystalline solids. Their reactivity is generally similar to the reactivity of azidobenziodoxoles. In particular, amidobenziodoxoles (**58-62**) can be used as amidating reagents toward polycyclic alkanes under radical conditions. For example, reagent (**59**) reacts with adamantane in chlorobenzene at 100-105°C in the presence of a catalytic amount of benzoyl peroxide to afford 1-amidoadamantane (**63**) in moderate yield (Fig. **19**) [72].

2.6 Cyanobenziodoxoles

Cyanobenziodoxoles (**64-66**) were synthesized independently in our laboratory [73, 74] and by Kita and coworkers [46]. These compounds can be prepared in one step by the reaction of cyanotrimethylsilane with the respective hydroxybenziodoxoles (**46**) (Fig. **20**) [73, 74], or from acetoxybenziodoxole and cyanotrimethylsilane [46].

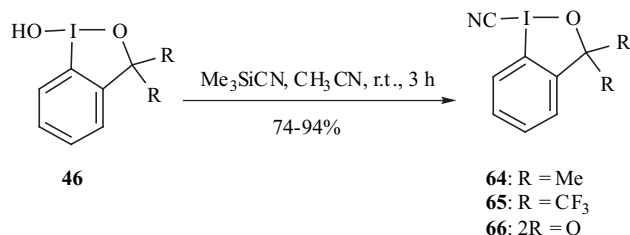


Fig. (20).

All three products (**64-66**) were isolated as thermally stable, white, microcrystalline solids. Structures of two of them (**65** and **66**) were unambiguously established by a single-crystal X-ray analysis [46, 74]. In particular, structural data for (**65**) revealed a distorted T-shaped geometry expected for hypervalent iodine with an endocyclic C-I-O bond angle of 78.2° and a NC-I-O bond angle of 169.5° [74]. The lengths of the bonds to the iodine atom, I-CN (2.167 Å), I-O (2.117 Å), and I-Ar (2.112 Å), are within the range of typical single covalent bond lengths in non-cyclic organic derivatives of polyvalent iodine.

Chemical reactivity of cyanobenziodoxoles (**64-66**) is generally similar to that of azidobenziodoxoles, and they can be used as efficient cyanating reagents toward *N,N*-dialkylarylamines. In a typical example, reagent (**66**) reacts with *N,N*-dimethylanilines (**67**) in 1,2-dichloroethane at reflux to afford the respective *N*-cyanomethyl-*N*-methylanilines (**68**) in good yield (Fig. **21**) [73].

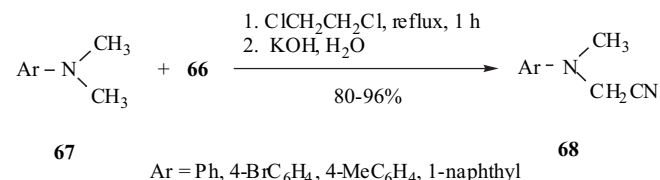


Fig. (21).

Recently, cyanobenziodoxole **66** was applied to the synthesis of *N*-cyanomethyl-*N*-cyclopropylamine, which is an important metabolite of the cyclopropylamine derived drugs [75].

2.7 Benziodazoles

In contrast to benziodoxoles, the five-membered iodine-nitrogen heterocycles, benziodazoles (**2**), have received much less attention and, moreover, their structural assignment in some cases was not reliable. The most important and readily available derivative of benziodazole, acetoxybenziodazole (**70**), was first prepared in 1965 by the peracetic oxidation of 2-iodobenzamide [35]. Based on the IR spectroscopy, the authors of this paper [35] incorrectly assigned the structure of *N*-acetyl-1-hydroxy-3-(1*H*)-1,2-benziodazole-3-one (**69**) for

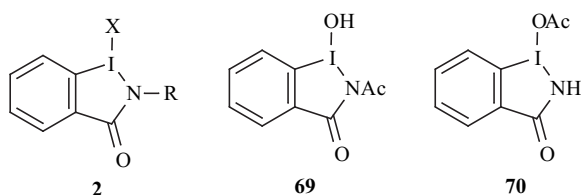


Fig. (22).

this compound. Structure (**69**) was also adopted in several other studies [46, 76, 77].

X-ray crystal analysis of acetoxybenziodazole (as a solvate with acetic acid) revealed its actual structure as (**70**), which was different from the previously adopted (**69**) [50]. The structural data for (**70**) showed the expected distorted T-shaped geometry with a N-I-O bond angle of 162.1°. The lengths of the bonds to the iodine atom, I-N (2.101 Å), I-O (2.34 Å), and I-C (2.106 Å), are all within the range of typical single covalent bonds in organic derivatives of polyvalent iodine and are in good agreement with the previously reported structures of chlorobenziodazoles [78, 79]. The results of *ab initio* molecular orbital calculations show that structure (**70**) is 6.31 kcal/mol more stable than (**69**) at the Hartree-Fock level of theory [49].

Acetoxybenziodazole (**70**) reacts at room temperature with azidotrimethylsilane to afford a novel azide (**71**) in the form of a yellow, microcrystalline precipitate (Fig. 23) [50]. Azide (**71**) has a reactivity similar to that of azidobenziodoxoles and can be used as an efficient azidating reagent toward dimethylanilines [50]. Amides and alcohols react with acetate (**70**) at room temperature after activation with trimethylsilyltriflate to afford the rearranged products (**72**) and (**73**) (Fig. 23), the structures of which were established by X-ray analysis [49]. A plausible mechanism of this rearrangement most likely includes ring opening and ring closure in the protonated benziodazole. Molecular orbital calculations indicate that the driving force of this novel rearrangement of benziodazoles to 3-iminiumbenziodoxoles is the greater thermodynamic stability of the *N*-protonated 3-iminobenziodoxoles (**72** and **73**) relative to the respective *O*-protonated benziodazole-3-ones by about 15 kcal/mol [49].

In a recent work [80], we reported the preparation and structure of new *N*-functionalized benziodazoles derived from natural amino acids. Acetoxybenziodazoles (**75**, **76**) were prepared by the peracetic acid oxidation of the readily available 2-iodobenzamides (**74**) (Fig. 24) and isolated in the form of

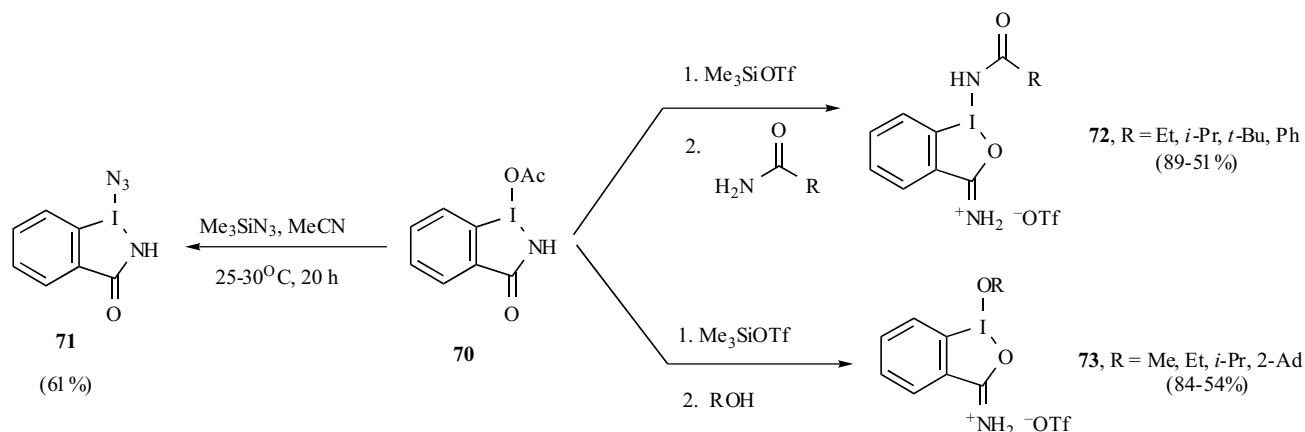


Fig. (23).

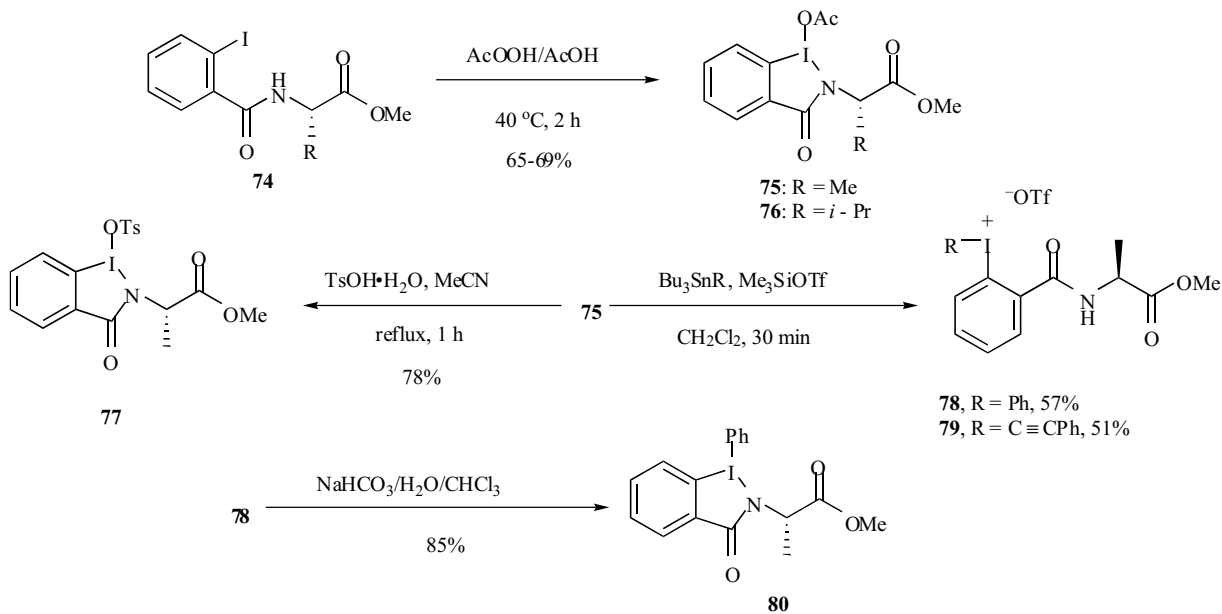


Fig. (24).

stable, white, microcrystalline solids. Acetoxybenziodazole (75) can be converted to the tosylate (77) by treatment with *p*-toluenesulfonic acid, or to iodonium salts (78, 79) by the reaction with tributylphenyltin or tributylphenylethynyltin in the presence of trimethylsilyl triflate.

The treatment of iodonium triflate (78) with an aqueous sodium bicarbonate resulted in a restoration of the benziodazole ring with the formation of a novel phenylbenziodazole (80) (Fig. 24). X-ray crystallographic analysis of (80) shows that the benziodoxole ring system is essentially planar and has a relatively long I–N bond of 2.445 Å. This value is significantly larger than that of the analogous I–N bond in acetoxybenziodazole (70) (Fig. 22), which is indicative of a substantial ionic character of the I–N interaction in (80). Overall, the geometry of (80) is similar to that observed for the previously reported structure of phenylbenziodoxole [80].

Recently, we have discovered a novel self-assembly of organoiodine(III) molecules into chiral and optically pure hypervalent iodine macrocycles (83, Fig. 25), which is directed by secondary bonding between hypervalent iodine and oxygen atoms of the amino acid fragment [81]. Macrocyclic products (83) were prepared by the oxidation of the corresponding *N*-(2-iodobenzoyl) amino acids (81) with dimethyldioxirane in 76–90% yields. It is assumed that the initial products in this reaction are the monomeric amino acid derived benziodazoles 82, subsequent trimerization of which affords the final products 83 (Fig. 25).

The structures of macrocycles (83c) and (83d) were established by X-ray analysis. Molecule (83) consists of a slightly distorted planar macrocyclic system with three oxygens of the amino acid carboxyls inside the ring and all three alkyl groups above the plane. Each iodine atom is covalently bonded to carbon (I–C = 2.092 Å) and nitrogen

(I–N = 2.064 Å) and has three longer intramolecular contacts with oxygen atoms (I–O = 2.368, 2.524, and 2.877 Å). With the consideration of primary and secondary bonds, the iodine atoms in (83) have a pentagonal-planar geometry, which is analogous to that found in the solid state for $\text{PhI}(\text{OAc})_2$ [81]. As a result of the central oxygens, the electron rich cavity of macrocycles (83) is suitable for complexation of metal cations. Specifically, ESI-MS data indicate that macrocycles (83) can selectively form complexes with sodium cations in the presence of K^+ , Li^+ , Ag^+ or Pb^{2+} [81]. The self-assembly of monomeric benziodazoles (82) into macrocyclic molecules (83) was studied using molecular orbital calculations [82]. The driving force for the self-assembly is the formation of secondary bonding interactions between molecules and a rearrangement of primary and secondary bonding around iodine to place the least electronegative substituent in the equatorial position for every iodine in the trimer.

3. FIVE-MEMBERED IODINE(V) HETEROCYCLES

The most important representative of pentavalent iodine heterocycles, 2-iodoxybenzoic acid (IBX, 84), was first described in 1893 by Hartman and Mayer [83]. Similar to 2-iodosylbenzoic acid (3) (see section 2.1), IBX has the actual structure of the cyclic benziodoxole oxide (1-hydroxy-1-oxo-1*H*-1 λ^5 -benzo[*d*][1,2]iodoxol-3-one according to the IUPAC nomenclature), as determined by X-ray structural analysis [84, 85]. Most commonly IBX is prepared by the oxidation of 2-iodobenzoic acid with potassium bromate in aqueous solution of sulfuric acid [86]. IBX was reported to be explosive under excessive heating or impact [87], but Dess and Martin suggested that the explosive properties of some samples were due to the presence of bromate or other impurities [88]. An alternative preparation of IBX involves

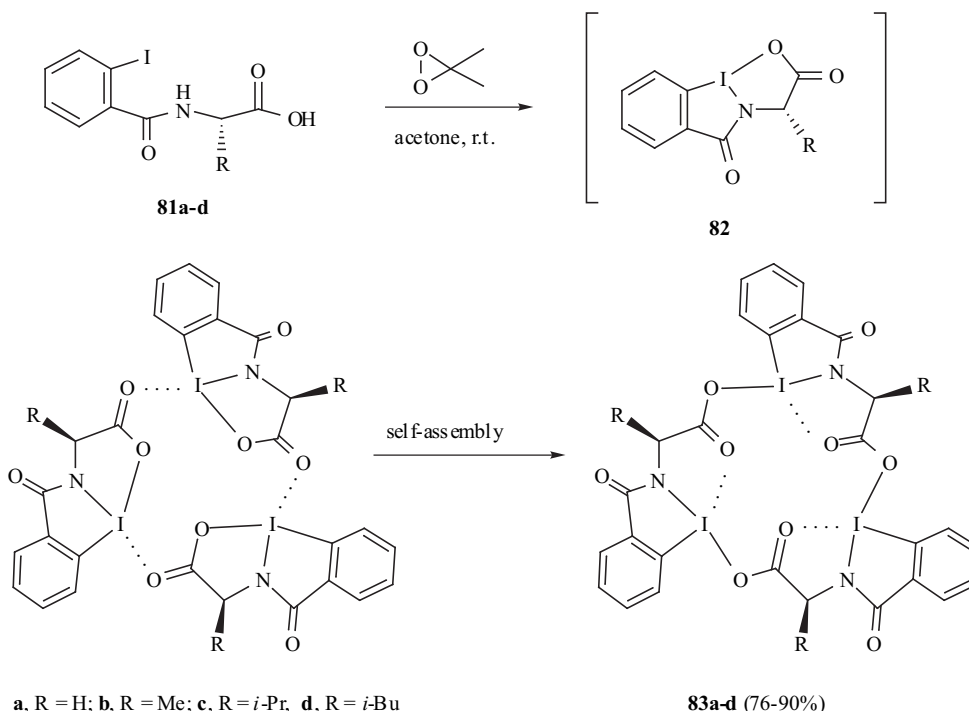


Fig. (25).

oxidation of the respective 2-iodobenzoic acid with excess peracetic acid or aqueous sodium hypochlorite [89]. A new, convenient procedure for the preparation of IBX (**84**) by the oxidation of 2-iodobenzoic acid with OXONE[®] (Fig. 26) was recently reported by Santagostino and co-workers [90]. IBX samples, prepared by the oxidation of 2-iodobenzoic acid, usually contain a mixture of the powder and the macrocrystalline forms. A detailed X-ray diffraction study of both forms of IBX was published by Stevenson and co-workers [91].

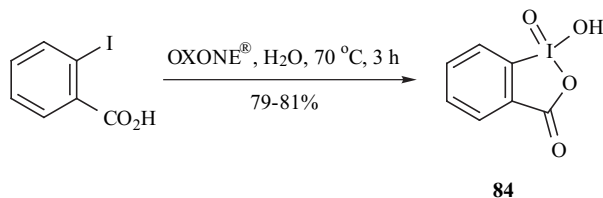


Fig. (26).

In 1983 Dess and Martin have first reported the preparation of triacetoxybenziodoxole (**85**) by heating IBX with acetic anhydride to 100 °C [92]. In the following years, the triacetate (**85**), has emerged as the reagent of choice for the oxidation of alcohols to the respective carbonyl compounds [93], and in the present literature it is commonly referred to as Dess-Martin periodinane (DMP). In 1994 Meyer and Schreiber have further investigated the mechanism of oxidations with DMP and have found that the oxidation of alcohols can be significantly accelerated by addition of water to the solution of DMP in dichloromethane immediately before or during the reaction [94]. An improved procedure for the preparation of DMP (**85**) consists in the reaction of IBX with acetic anhydride in the presence of *p*-toluenesulfonic acid (Fig. 27) [95].

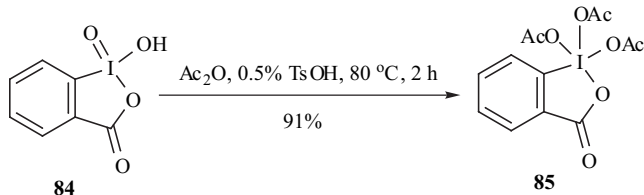


Fig. (27).

The seminal works of Dess and Martin [88, 92, 94] initiated a dramatic interest in the synthetic uses of pentavalent iodine heterocycles.

3.1 IBX and Analogous Reagents

IBX and its analogs have attracted increasing interest as mild and selective oxidizing reagents. Solutions of IBX in DMSO are useful for the clean oxidation of alcohols to carbonyl compounds even in the presence of other functional groups [96-108]. Specifically, the allylic alcohols **86** are selectively oxidized by IBX to ketones **87** in high yield (Fig. 28) [96].

The oxidation of alcohols **88** under similar conditions selectively affords 5-monosubstituted 3-acyl-4-*O*-methyl tetronates **89** (Fig. 29), which are structurally similar to the tetrodecamycin antibiotics [97].

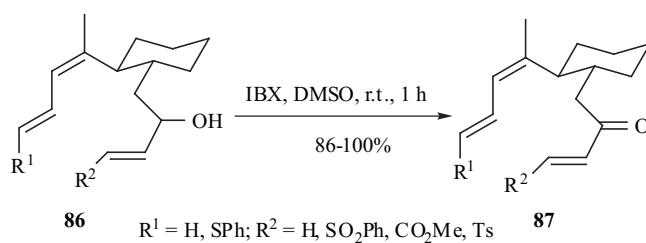


Fig. (28).

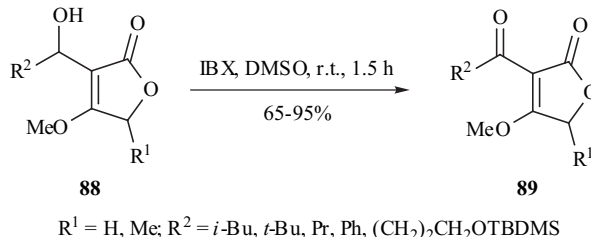


Fig. (29).

The IBX oxidation of diol **90** was applied in the synthesis of the functionalized hexahydroanthracene dione **92** (Fig. 30), a model for the D ring of taxoids [98].

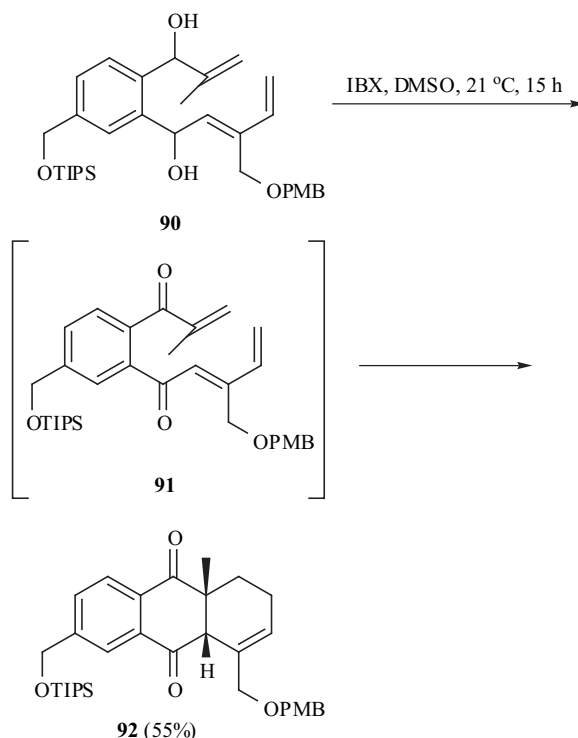


Fig. (30).

Likewise, the oxidation of diol **93** affords hemiacetal **94** (Fig. 31), a key precursor to the antifungal agent GM222712 [99].

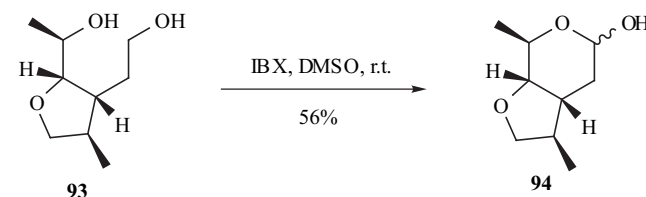


Fig. (31).

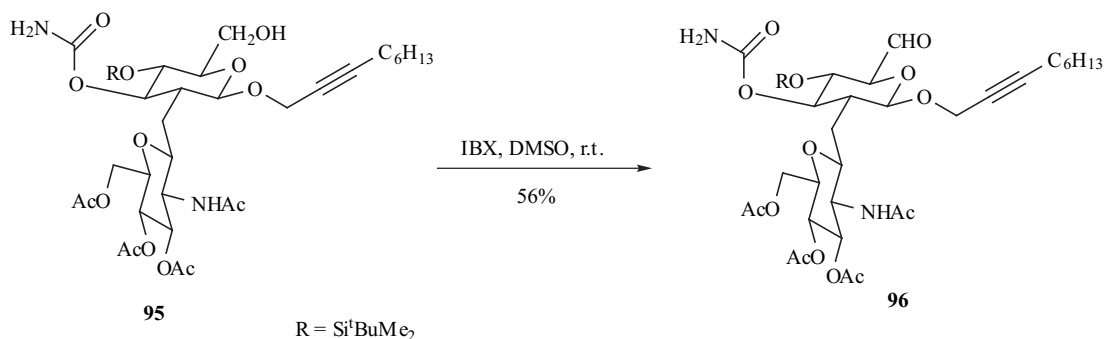


Fig. (32).

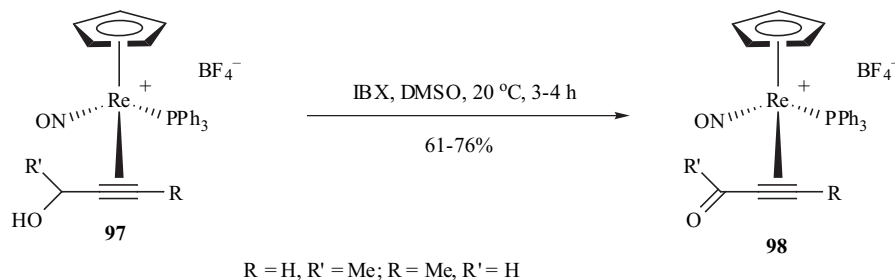


Fig. (33).

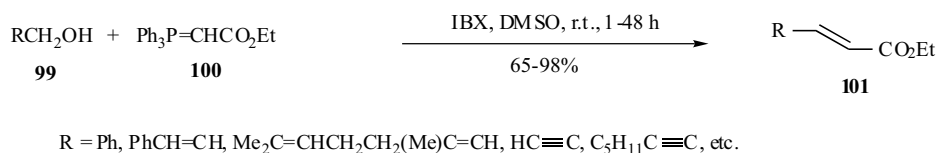


Fig. (34).

The IBX oxidation of carbohydrate **95** was used in the synthetic studies of moenomycin A disaccharide analogs (Fig. 32) [100].

The chiral rhenium complexes of allylic and propargylic alcohols **97** are selectively oxidized by IBX to the respective carbonyl derivatives **98** in good yields under mild conditions (Fig. 33) [101].

Benzylic, allylic, and propargylic alcohols, as well as diols, can be oxidized with IBX in the presence of the stabilized Wittig ylide **100** to generate α,β -unsaturated esters **101** in one pot (Fig. 34) [102]. This is a useful procedure when the intermediate aldehydes are unstable and difficult to isolate.

The oxidation of alcohols with IBX in DMSO was also used in the development of a new silyl ether linker for solid-phase organic synthesis [103], in the kinetic study of organic reactions on polystyrene grafted microtubes [104], and in the total synthesis of a cyclic depsipeptide somamide A [105].

IBX is especially useful for the oxidation of glycols. In contrast to the Dess-Martin periodinane, which generally cleaves the glycol C–C bond, IBX in DMSO oxidizes them to α -ketols [106, 107] or α -diketones [108, 109]. The mechanism of the alcohol and 1,2-diol oxidation by IBX and DMP has been examined by ¹H NMR spectroscopy [109].

Practical usefulness of IBX in general is significantly restricted by low solubility in most organic solvents except

DMSO. However, in several recent reports [110-113] it has been demonstrated that IBX can be used as effective oxidant in other than DMSO solvents. More and Finney have found that primary and secondary alcohols can be oxidized into the corresponding aldehydes or ketones in excellent yields (90-100%) by heating a mixture of alcohol and IBX in organic solvent followed by filtration of insoluble byproducts [110]. This method was recently used for the efficient preparation of the ribosyl aldehyde (**103**) (Fig. 35), the key intermediate in the stereoselective synthesis of the core structure of the polyoxin and nikkomycin antibiotics [111].

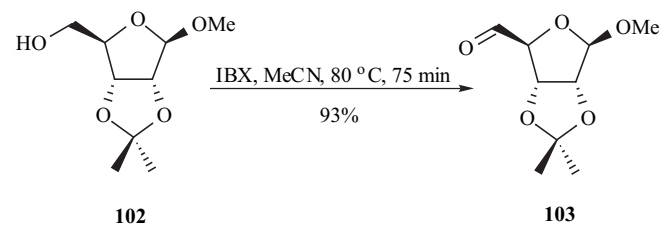


Fig. (35).

A mild and efficient procedure for the oxidation of alcohols with IBX catalyzed by β -cyclodextrin in aqueous acetone was developed by Rao and co-workers [112]. This oxidation proceeds at room temperature and affords the respective carbonyl compounds in excellent yields (85-98%) from a various alcohols. The oxidation of diols (**104**) under these conditions selectively affords α -ketols (**105**) (Fig. 36).

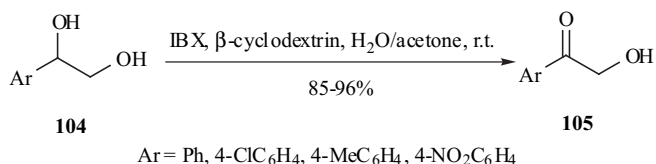


Fig. (36).

Chen and co-workers reported a mild, efficient, and eco-friendly procedure for the oxidation of alcohols with IBX in ionic liquid 1-butyl-3-methylimidazolium chloride and water [113]. Simply stirring a solution of the alcohol and IBX in 1-butyl-3-methylimidazolium chloride/water at room temperature followed by extraction with ether or ethyl acetate and removal of the solvent gives excellent yields (88-99%) of the corresponding carbonyl compounds. No overoxidation to acids was observed in the case of aldehyde products, and various functionalities such as methoxy and nitro groups, double bonds, and a furan ring can tolerate the oxidation. The oxidation of glycols under these conditions affords α -ketols if equimolecular amounts of IBX is used, or α -diketones in the presence of excessive IBX.

An interesting IBX-mediated oxidation of primary alcohols or aldehydes to carboxylic acids was developed by Giannis and co-workers [114]. In this procedure, the oxidation of alcohol is carried out in the presence of a suitable *O*-nucleophilic additive, such as 2-hydroxypyridine, 1-hydroxybenzotriazole, or *N*-hydroxysuccinimide. The generality of this procedure was demonstrated on a variety of aliphatic, allylic, and benzylic alcohols.

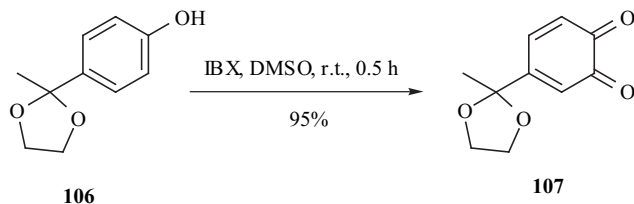


Fig. (37).

The practical value of IBX as a reagent was recently extended to a variety of other synthetically useful oxidative

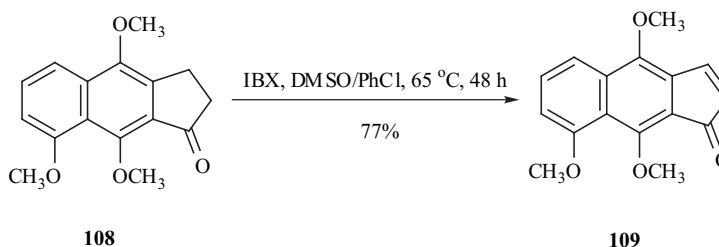
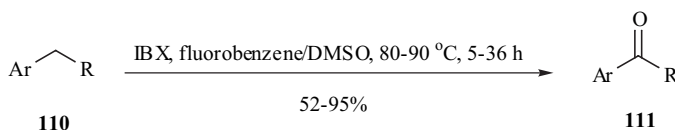


Fig. (38).



Ar = Ph, 4-*t*-BuC₆H₄, 2-MeC₆H₄, 3-IC₆H₄, 4-BrC₆H₄, 3,4-(MeO)₂C₆H₃, 2-PhC₆H₄, 4-(4-pyridyl)C₆H₄, etc.
R = H, C₃H₇, etc.

Fig. (39).

transformations. IBX in DMF has been found to be an excellent reagent for the oxidation of various phenols to *o*-quinones [115]. This procedure was recently applied for the oxidation of phenol (**106**) to quinone (**107**) (Fig. 37), the key intermediate in total synthesis of a novel cyclooxygenase-inhibitory stilbenolignan (\pm)-aiphanol [116].

In a series of papers, Nicolaou and coworkers have demonstrated the utility of IBX for the one-step synthesis of α,β -unsaturated carbonyl systems from saturated alcohols and carbonyl compounds [117-121], for the selective oxidation of the benzylic carbon [122], for the oxidative cyclization of anilides and related compounds [123-126], and for the synthesis of amino sugars and libraries thereof. Various alcohols, ketones, aldehydes, or silyl enol ethers are oxidized to the corresponding α,β -unsaturated species in one pot using IBX or a complex of IBX with *N*-oxides under mild conditions [117-121]. A similar dehydrogenation of benz[*f*]indanone (**108**) with IBX in DMSO/chlorobenzene (Fig. 38) was recently used in the synthesis of kinamycin precursors [127].

IBX is an efficient and a selective reagent for the oxidation of benzylic and other similarly activated positions (Fig. 39) [122]. This reaction is quite general and is not affected by the presence of water, *ortho*-substituents, or halogen substituents. Overoxidation to the corresponding carboxylic acids is not observed even in the presence of electron-rich substituents.

A variety of new heterocycles (**113**) can be synthesized by the treatment of unsaturated aryl amides, carbamates, thiocarbamates, and ureas with IBX (Fig. 40) [123, 124]. The mechanism of this reaction has been investigated in detail [125]. On the basis of solvent effects and D-labeling studies, it was proposed that the IBX-mediated cyclization of anilides in THF involves an initial single electron transfer to a THF-IBX complex followed by deprotonation, radical cyclization, and concluding termination by hydrogen abstraction from THF.

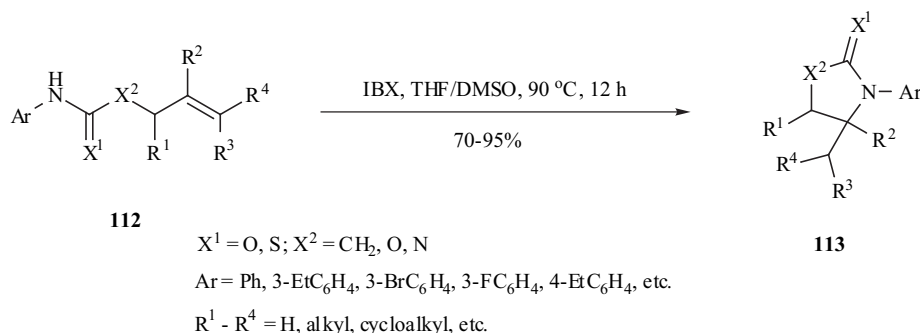


Fig. (40).

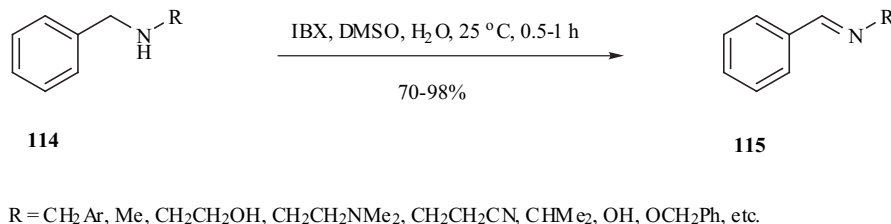


Fig. (41).

A similar IBX-mediated cyclization was applied in the synthetic protocol for the stereoselective preparation of amino sugars [126].

Nicolaou and coworkers have recently developed a general IBX-induced procedure for the generation of imines (**115**) from secondary amines (**114**) in notably high yields (Fig. 41) [127]. Furthermore, various nitrogen heterocycles can be obtained by a similar oxidation of cyclic amines with IBX in DMSO at 45 °C [127].

Several research groups have independently demonstrated that IBX is an efficient reagent for cleavage of dithianes to the corresponding carbonyl compounds under mild conditions [128-130]. In particular, Wu and coworkers have found that various dithianes and dithiolanes at benzylic or allylic carbons can easily be hydrolyzed by IBX in DMSO containing traces of water (Fig. 42) [129]. Likewise, various aromatic thioacetals and thioketals can be hydrolyzed to the

respective carbonyl compounds using IBX in the presence of β -cyclodextrin in water [130].

IBX can be used as an efficient and selective reagent for the oxidative cleavage of oximes and tosylhydrazones to yield the corresponding carbonyl compounds under mild conditions in high yields [131]. IBX can oxidize thiols to the corresponding disulfides [132] and, in the presence of tetraethylammonium bromide, it can selectively oxidize disulfides to the respective sulfoxides [133]. As it was shown in the hydrolysis of phosphonofluoridates and non-toxic stimulants, IBX can be used as a catalyst with OXONE[®] being a stoichiometric oxidant [134].

Several analogs of IBX have been reported in the literature [135-147]. Bis(trifluoromethyl)benziodoxole oxide (**118**), which was originally reported by Martin and coworkers [88], is a synthetically useful, powerful oxidizing reagent with a similar to IBX and DMP applications. Grieco

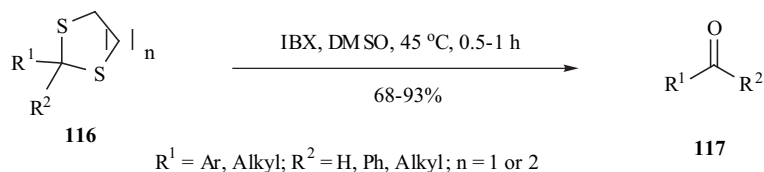


Fig. (42).

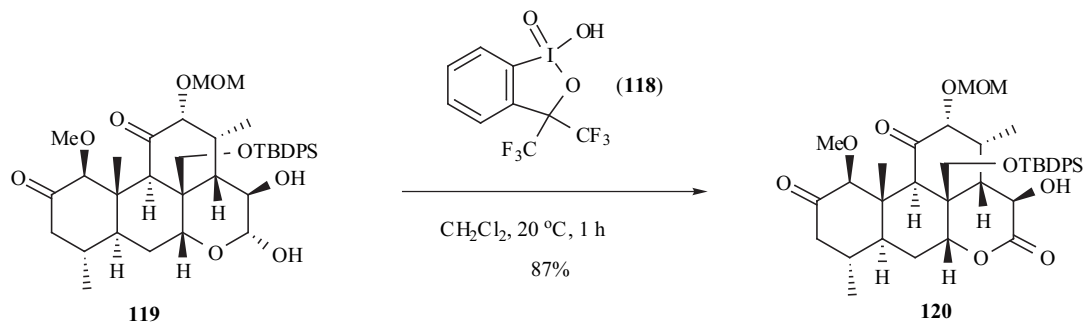


Fig. (43).

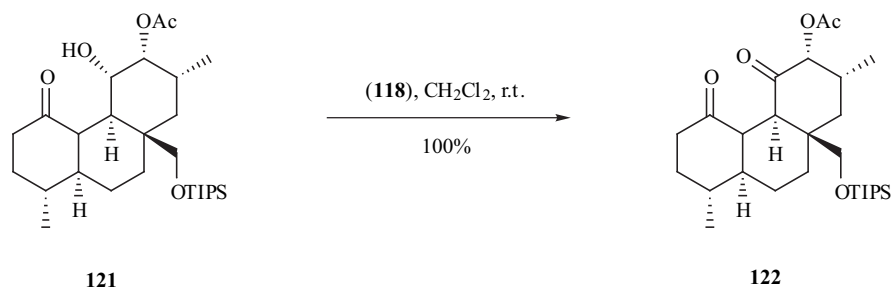


Fig. (44).

and co-workers have successfully applied this reagent in the oxidation of diol (**119**) to lactone (**120**) (Fig. 43), which is an important intermediate in the total synthesis of (-)-glaucarubolone [135]. Attempts to use the Dess-Martin periodane, as well as many other oxidizing reagents, in this oxidation (Fig. 43) led only to cleavage products, but not the desired lactone (**120**).

Reagent (**118**) was used in the total syntheses of des-D-chaparrinone and bruceoside C [136, 137]. Specifically, the oxidation of the alcohol (**121**) with reagent (**118**) under mild conditions quantitatively afforded ketone (**122**) (Fig. 44), an important intermediate product in the synthesis of des-D-chaparrinone [136].

Moody and Lack used reagent (**118**) under similar conditions in the synthesis of benzofuranone derivative (**124**) (Fig. 45), a potential intermediate for the synthesis of the marine natural product diazonamide A [138].

Parlow and coworkers performed the oxidation of various primary and secondary alcohols with reagent (**118**) and developed a simple and efficient methodology for sequestering by-products and excess starting reagent from the solution-phase using a novel thiosulfate resin [139].

Thottumkara and Vinod have reported the preparation of the water-soluble analog of IBX, *m*-iodoxyphthalic acid (mIBX, **126**), which is useful for the oxidation of alcohols (**125**) to the corresponding carbonyl compounds (**127**) in aqueous solutions (Fig. 46) [140].

The new cyclic derivatives of pentavalent iodine, benziodazole oxides (**129**), were prepared by the oxidation of the readily available 2-iodobenzamides (**128**) with potassium bromate (Fig. 47) [141].

Benziodazole oxides (**129**) can find practical application as selective, chiral oxidizing reagents in organic synthesis.

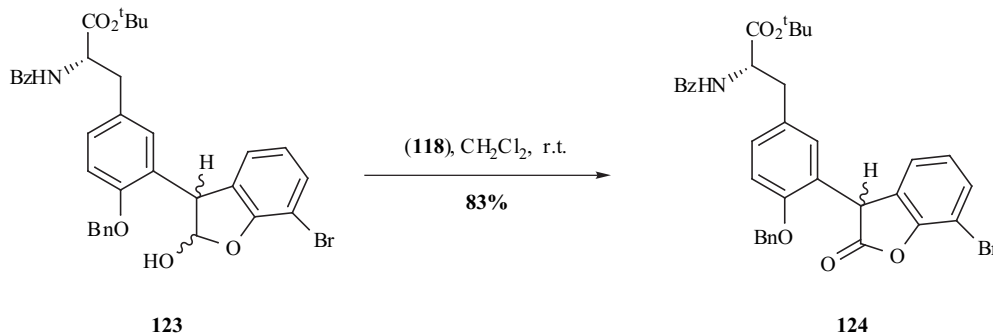


Fig. (45).

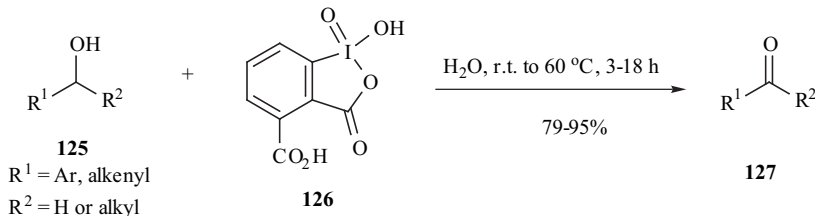


Fig. (46).

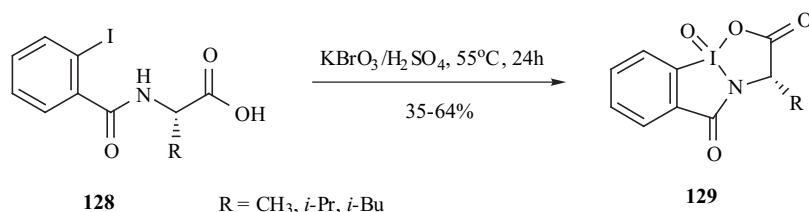


Fig. (47).

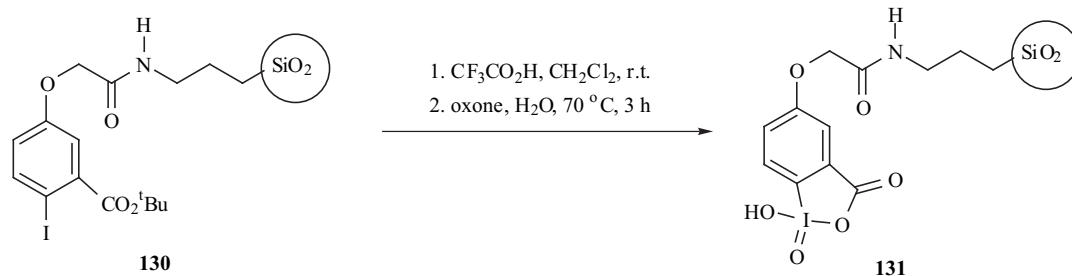


Fig. (48).

Preliminary results indicate that reagents (**129**) can selectively oxidize primary alcohols to aldehydes in chloroform at 50 °C. Under similar conditions, reagents (**129**) oxidize organic sulfides to sulfoxides in almost quantitative yield. Oxidation of non-symmetric sulfides affords chiral sulfoxides with moderate enantioselectivity (11-16% ee) [141].

Quideau and co-workers reported a new stabilized formulation of IBX (SIBX) useful for various oxidation reactions [142]. SIBX, a nonexplosive mixture comprised of benzoic acid, isophthalic acid, and IBX, is a safe and effective oxidant for the oxidation of allylic, benzylic, aliphatic and alicyclic alcohols to ketones and aldehydes in a variety of solvents such as DMSO, THF, or ethyl acetate. The yields of aldehydes and ketones are comparable to those obtained with either IBX or DMP [142].

Several research groups have recently reported the synthesis and oxidative reactions of the polymer-supported analogs of IBX [143-147]. In particular, Giannis and Mülbauer prepared the aminopropylsilica gel based reagent (**131**) by the OXONE[®] oxidation of the polymeric precursor (**130**) (Fig. 48) [143, 144].

Various primary and secondary alcohols can be oxidized by reagent (**131**) to the respective carbonyl compounds in excellent yields at room temperature in THF under heterogeneous conditions. The products of oxidation can be easily purified by filtration, and the reagent can be regenerated by oxidation with OXONE[®] without any loss of activity [143, 144].

The polystyrene based polymeric analog of IBX (**133**) was independently reported by the research groups of Rademann [145] and Janda [146]. Polymeric reagent (**133**) was prepared by the oxidation of resin (**132**) with an equimolar mixture of tetrabutylammonium OXONE[®] and methanesulfonic acid (Fig. 49). Polymer (**133**) was characterized by IR spectroscopy, elemental analysis, and MAS-NMR spectroscopy [145].

Reagent (**133**) oxidizes various primary, secondary, benzylic, allylic, terpene alcohols, and the carbamate-

protected aminoalcohols to afford the respective aldehydes or ketones in excellent yields and purities. Resin (**133**) can be recycled by repeated oxidation after extensive washings [145].

A similar polymer-supported IBX reagent based on poly(*p*-methylstyrene) was recently reported by Sutherland and co-workers [147].

3.2 Dess-Martin Periodinane

In recent years, Dess-Martin periodinane [DMP; 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one, **85**, see Fig. 27] has emerged as the reagent of choice for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively. The mild reaction conditions (room temperature and neutral pH), high chemoselectivity, and convenience of use have made this reagent especially suitable for the oxidation of substrates containing sensitive functional groups. Moreover, DMP is currently commercially available from Sigma-Aldrich and other chemical companies. The synthetic applications of DMP were recently highlighted in two overviews [148, 149].

Due to the unique oxidizing properties and convenience of use, DMP is widely used in the synthesis of biologically important natural products. Recently DMP was used in key oxidation steps in the total syntheses of cyclotheonamide B [150], (±)-deoxypreussomerin A [151], racemic brevioxime [152], erythromycin B [153], (+)-discodermolide [154], (+)-cephalostatin 7 [155], (+)-cephalostatin 12 [155], (+)-ritterazine K [155], 3-*O*-galloyl-(2*R*,3*R*)-epicatechin-4β,8-[3-*O*-galloyl-(2*R*,3*R*)-epicatechin] [156], fredericamycin A [157], indolizidine alkaloids (-)-205A, (-)-207A, and (-)-235B [158], 1,19-aza-1,19-desoxy-avermectin B_{1a} [159], angucycline antibiotics [160], tricyclic β-lactam antibiotics [161], the platelet aggregation-inhibiting γ-lactam PI-091 [162], cycloproparadicicol [163], columbetdione [164], didehydro pristinamycins [165], and pseudolaric acids [166]. It was emphasized in many cases that DMP was the only reagent applicable in these oxidations, while other common oxidation methods, including Swern oxidation, Jones

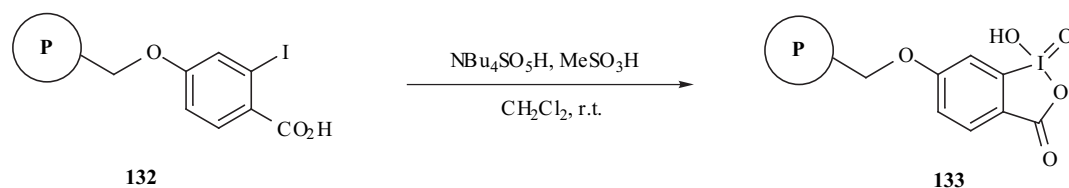


Fig. (49).

oxidation, and other chromium based procedures, failed [160, 161].

In the numerous synthetic studies, it has been demonstrated that DMP can be used for the selective oxidation of alcohols containing sensitive functional groups, such as, unsaturated alcohols [167-177], carbohydrates, polyhydroxy derivatives and polyethers [178-186], silyl ethers [187, 188], amines and amides [189-198], tetrazines [199], various nucleoside derivatives [200-204], selenides [205, 206], tellurides [207], phosphine oxides [208-210], homoallylic and homopropargylic alcohols [211], heteroaromatic homoallylic alcohols [212], and fluoroalcohols [213-218]. Several representative examples of these oxidations are shown in Figures 50-53. Specifically, the functionalized allylic alcohols (**134**), the Baylis-Hillman adducts of aryl aldehydes and alkyl acrylates, are efficiently oxidized with DMP to the corresponding α -methylene- β -keto esters (**135**) (Fig. 50) [173]. The attempted Swern oxidation of the same adducts (**134**) resulted in S_N2' -type substitution of the allylic hydroxyl group by chloride.

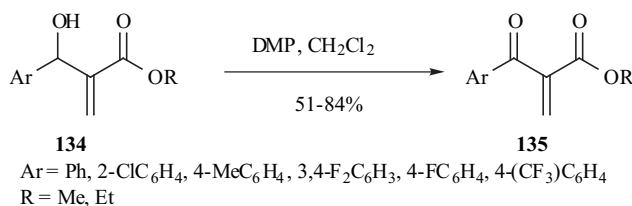


Fig. (50).

Cyclic enecarbamates (**137**) were prepared in excellent yields by the oxidation of ω -hydroxycarbamates (**136**) with DMP followed by cyclocondensation-dehydration of the intermediate aminoaldehydes (Fig. 51) [196].

Depending on the length of the carbon tether, α,ω -diols (**138**) either afford cyclic acetoxy acetals (**139**) or dialdehydes (**140**) upon treatment with DMP (Fig. 52) [181]. In contrast, the treatment of 1,2-diols with DMP leads to the oxidative cleavage of the glycol bond [109, 135, 156].

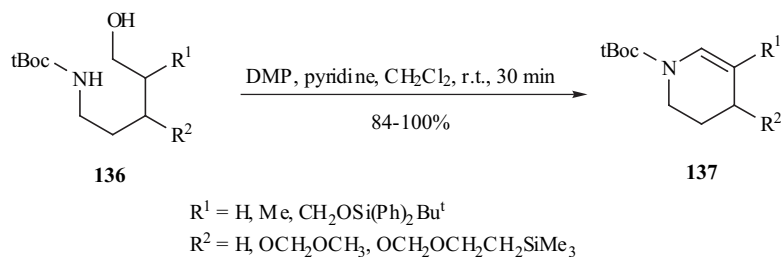


Fig. (51).

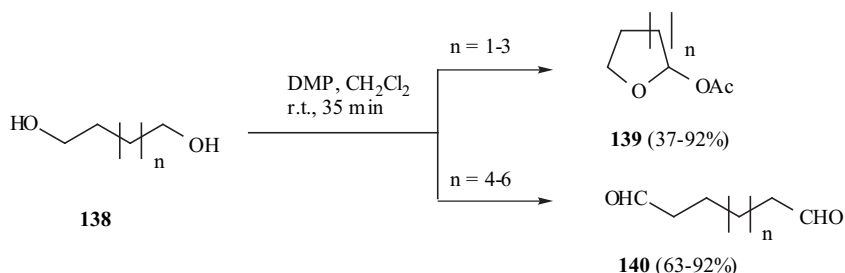


Fig. (52).

Polyfluorinated alcohols (**141**) can be selectively oxidized by DMP to the respective aldehydes (**142**) (Fig. 53) without the formation of dehydrofluorinated by-products [216-218].

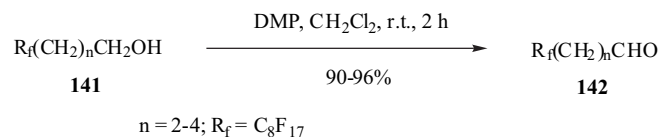


Fig. (53).

DMP is especially useful for the oxidation of the optically active, epimerization sensitive substrates without loss of enantiomeric excess [189, 214, 215, 219]. In a typical example, DMP was found to be a superior oxidant for the efficient, epimerization-free synthesis of optically active *N*-protected α -amino aldehydes (**144**) from the corresponding *N*-protected β -amino alcohols (**143**) (Fig. 54) [189]. In contrast, the Swern oxidation of amino alcohols (**143**) afforded products (**144**) of only 50-68% ee.

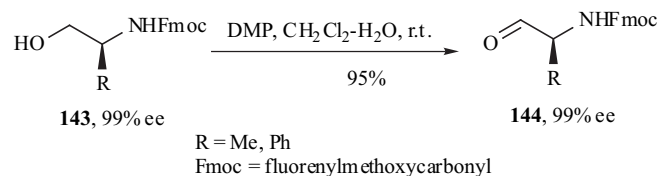


Fig. (54).

Primary alcohols can be oxidized with DMP in the presence of stabilized Wittig ylides to afford the respective α,β -unsaturated esters in one pot [205, 220, 221]. This is a useful procedure when the intermediate aldehydes are unstable and difficult to isolate. In a representative example, a highly unstable dialdehyde, 2-butyndial, was generated by the oxidation of propargylic diol (**145**) with DMP and trapped by Wittig ylide *in situ* to provide the adduct (**146**) as a 4:1 mixture of *trans-trans* and *trans-cis* isomers (Fig. 55) [220].

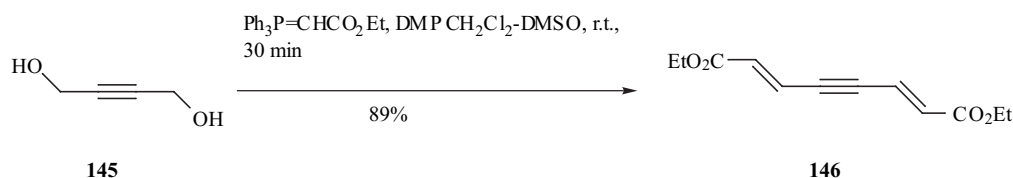


Fig. (55).

The practical value of DMP as a reagent was recently extended to a variety of other synthetically useful oxidative transformations [222-237]. DMP can be used as an efficient and selective reagent for the oxidative cleavage of oximes [222-225] and tosylhydrazones [225] to yield the corresponding carbonyl compounds under mild conditions in high yields. In a specific example, DMP oxidatively deoximates aldoximes as well as ketoximes (**147**) in very high yields, smoothly in short time, and under mild conditions (Fig. **56**) [223]. Deoxygenation occurs selectively in the presence of primary, secondary, and benzylic alcohols, *O*-methyl oximes, and acid-sensitive groups.

The oxidation of *N*-acyl hydroxylamines (**149**) with DMP generates the highly reactive acyl nitroso compounds (**150**), which can be trapped by conjugated dienes to produce the corresponding cycloadducts (**151**) (Fig. **57**) [226].

2-Hydroxy porphyrins and 2-aminoporphyrins (**152**), as well as 2,3-aminoporphyrins, are oxidized by DMP to porphyrin- α -diones (**153**) (Fig. **58**) [227-229]. This reaction

has been applied to the preparation of meso-functionalized porphyrin- α -diones, which are the basic building blocks for bis-porphyrin arrays [228].

DMP is an efficient reagent for cleavage of thioacetals and thioketals (**154**) to the corresponding carbonyl compounds (**155**) under mild conditions (Fig. **59**) [230]. In contrast to other existing methods, this protocol offers general reactivity, convenient reaction times, and compatibility with a wide range of functional groups including free primary and secondary alcohol functions.

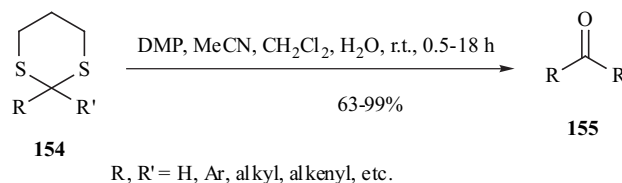
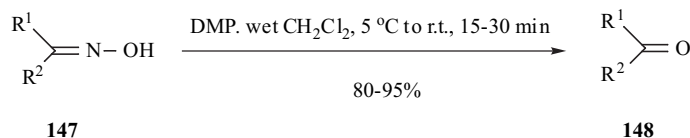


Fig. (59).



$\text{R}^1 = \text{Ph}, 4\text{-ClC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 2\text{-furyl},$
 $\text{PhCH}=\text{CH}, 4\text{-Me}_2\text{NC}_6\text{H}_4, \text{C}_5\text{H}_{11}, \text{C}_7\text{H}_{15}, \text{C}_9\text{H}_9, \text{PhC(O)}, \text{Ph}_2\text{CHCH}_2$
 $\text{R}^2 = \text{H}, \text{PhHC}=\text{CH}, \text{CO}_2\text{Me}, \text{Me}, (\text{CH}_2)_2\text{CO}_2\text{H}, \text{NH}_2$

Fig. (56).

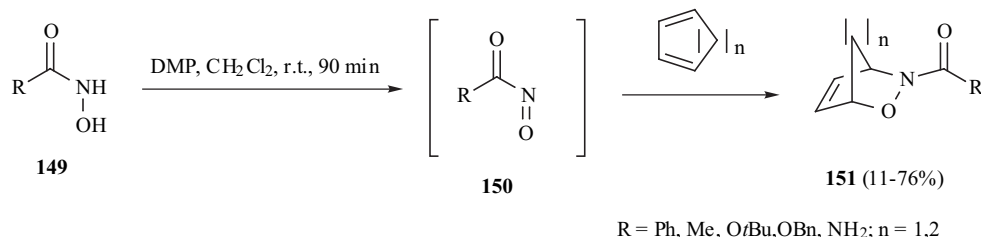


Fig. (57).

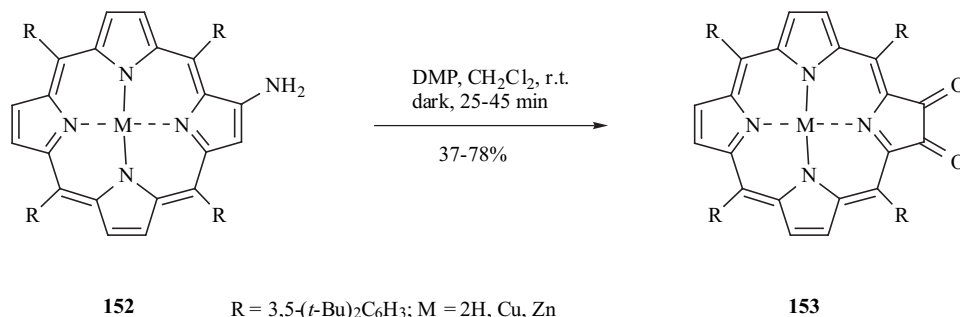


Fig. (58).

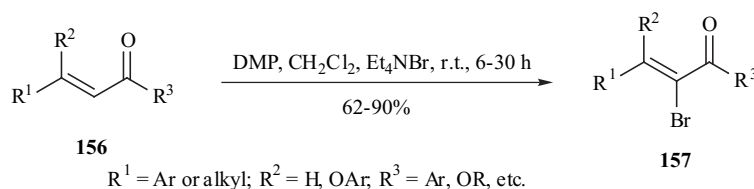


Fig. (60).

Akamanchi and co-workers developed a new one-step procedure for the preparation of α -bromo- α,β -unsaturated carbonyl compounds (**157**) in moderate to good yields from the corresponding carbonyl compounds (**156**) using DMP and tetraethylammonium bromide under neutral and mild reaction conditions (Fig. 60) [231].

Various acyl azides (**159**) can be prepared in one step from aldehydes (**158**) using Dess-Martin periodinane and sodium azide under mild conditions (Fig. 61) [232]. It is assumed that the mechanism of this reaction involves the initial formation of the unstable azidobenziodoxole from DMP and sodium azide followed by homolytic decomposition to generate an azido radical, which then azidonates the starting aldehyde via H-abstraction and coupling [232].

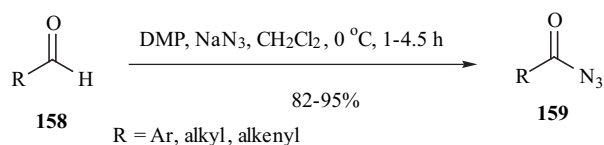


Fig. (61).

DMP has been employed in a simple and efficient approach to 1,3,5-trisubstituted 1,2,4-triazoles (**161**) via cyclization of 1,2,4-triazenes (**160**) (Fig. 62) [233]. This reaction proceeds under mild conditions and is compatible with various functional groups.

In a series of recent papers, Nicolaou and coworkers have demonstrated the utility of DMP for the selective oxidation of 4-substituted anilides **162** to *p*-quinones **163** (Fig. 63) and 2-substituted anilides **164** to *o*-azaquinones **165** (Fig. 64) [234-236]. The first process (Fig. 63) was applied to the short and efficient total synthesis of epoxyquinomycin B [234, 235], while the second type of oxidation (Fig. 64) allowed rapid access to complex analogs of pseudopterosin and elisabethin natural products [236].

Anilides with pendant double bonds (**166**) undergo stereoselective oxidative cyclization in the presence of DMP to give complex and diverse natural product-like polycycles (**167**) (Fig. 65) [237, 238]. A specific example of the oxidation of carbamates (**168**) leading to the benzomorfoline derivatives (**169**) is shown in Fig. 66.

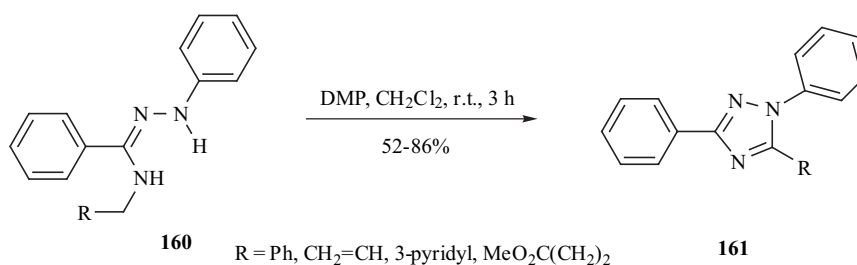


Fig. (62).

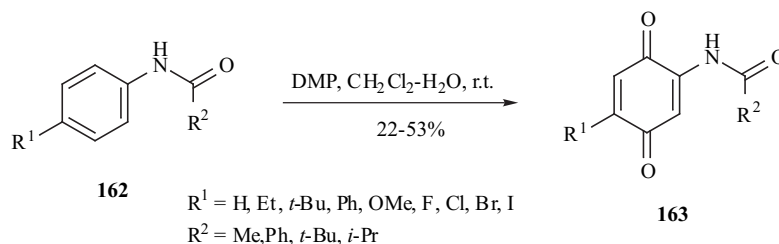


Fig. (63).

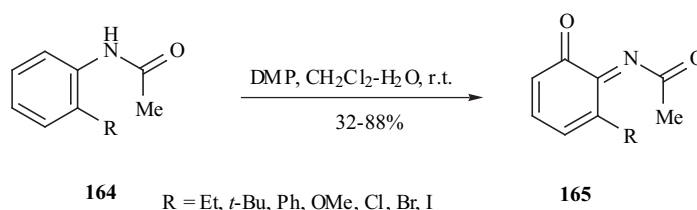


Fig. (64).

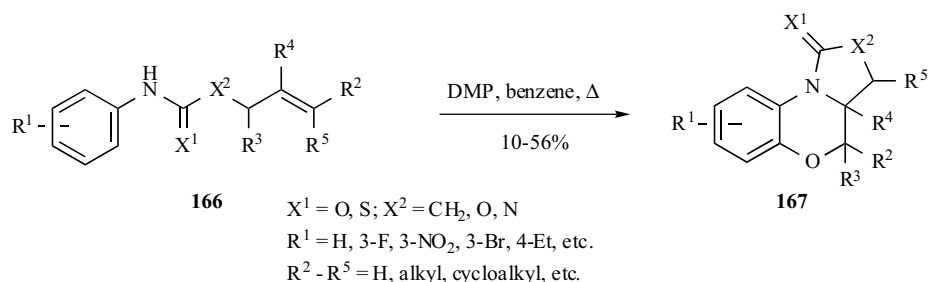


Fig. (65).

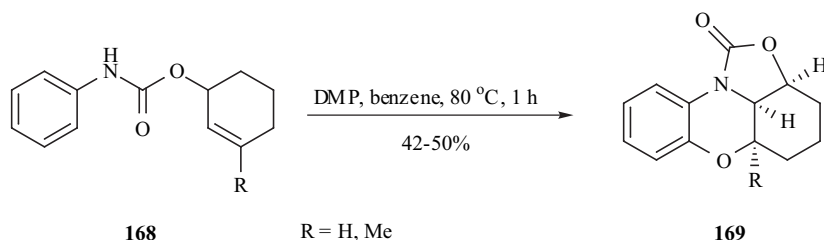


Fig. (66).

This oxidative cyclization (Fig. 66) is proposed to occur by the initial *ortho* directed oxidation of the anilide (**168**) to give an *ortho*-hydroxylated benzene ring which is further oxidized to the quinone imine; the intramolecular Diels-Alder cyclization of the quinone imine with the pendant alkene gives the final product (**169**) [237].

The unique oxidizing properties of DMP can be best illustrated by its wide application in the total synthesis of the CP-molecules recently published by Nicolaou and coworkers [239-241].

3.3 Pseudo-Benziodoxoles

Aryliodosyl and aryliodol derivatives bearing an appropriate substituent in the *ortho*-position to the iodine, are characterized by the presence of a planar, pseudocyclic benziodoxole structural moiety due to a strong intramolecular secondary bonding between the hypervalent iodine center and the oxygen atom in the *ortho*-substituent.

The distance between the iodine and oxygen atoms in pseudo-benziodoxoles varies in a range from 2.47 Å [242, 243] to 2.7 Å [244-248], which is comparable with the I-O bond length in benziodoxoles (**1**) from 2.11 Å to 2.48 Å (see section 2 of this review). Compared to the non-cyclic aryliodosyl and aryliodol derivatives, pseudo-benziodoxoles have much better solubility, which is explained by a partial disruption of their polymeric nature due to the redirection of secondary bonding [244-248]. In recent years, pseudo-benziodoxoles have found increasing practical application in organic synthesis as efficient oxidizing reagents.

Wirth and coauthors reported the preparation of a series of *ortho*-substituted chiral hypervalent iodine reagents (**174**) starting from the corresponding arylhalides as shown in Figure 67 [242, 243, 249]. The structure of compound (**174**, $R = \text{H}$) was established by X-ray analysis. Within this molecule, an intramolecular close contact between the iodine center and the oxygen atom of the methoxy group (2.47 Å) affords the pseudo-benziodoxole ring.

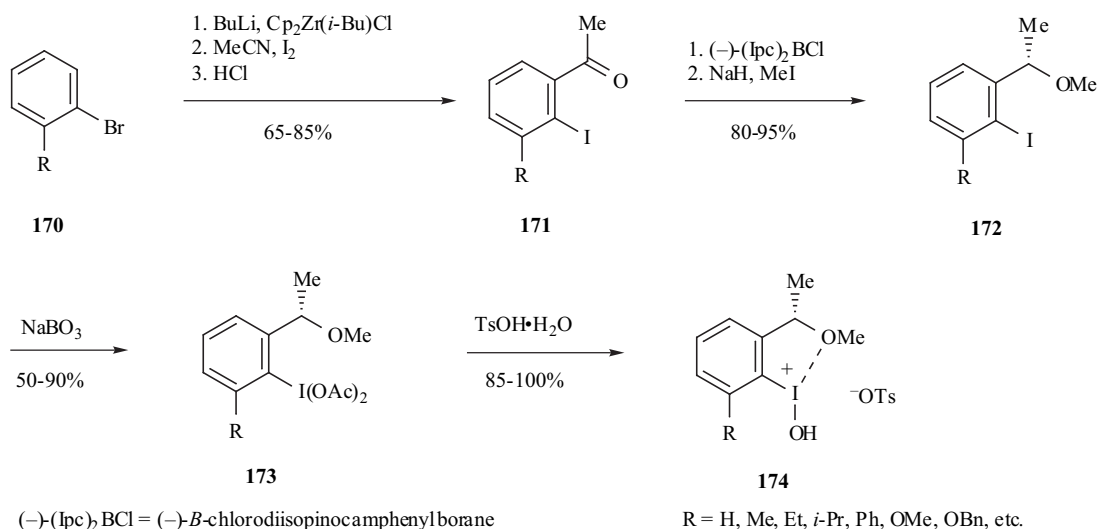


Fig. (67).

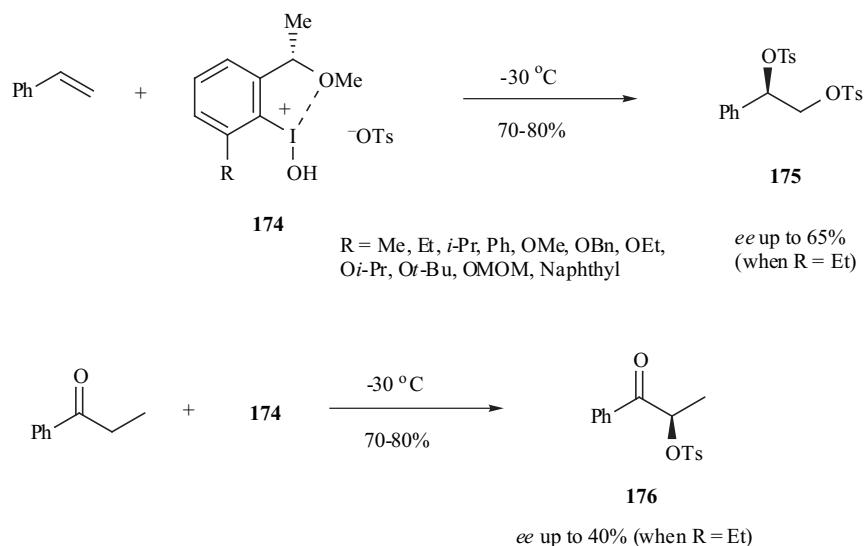


Fig. (68).

Compounds (**174**) were evaluated as enantioselective electrophilic reagents towards alkenes and ketones. Enantioselectivities as high as 65% have been achieved in the dioxysylation of styrene and of up to 40% in the oxytosylation of propiophenone (Fig. 68). The maximum selectivity is observed in the reactions of *ortho*-ethyl compounds (**174**), with lower selectivity being observed for reagents (**174**) bearing both smaller and larger substituents R. X-ray structure analysis and *ab initio* calculations have been used to develop a model for rationalizing the stereoselectivities in the reactions of chiral hypervalent iodine reagents (**174**). In this model, high enantiomeric excess in the reaction correlates with the relative population of a conformation in which a methyl group on the asymmetric carbon atom is in the axial position [242].

Protasiewicz and coworkers have reported the preparation and X-ray structure of the monomeric iodosylarene (**179**) (Fig. 69), in which the intramolecular secondary I...O bond replaces the intermolecular interactions that are typical of polymeric iodosylbenzene [244, 245, 250].

Iodosylarene (**179**) is readily soluble in organic solvents (up to 0.08 M in chloroform) and can be analyzed by NMR in solution [245]. Single crystal X-ray analysis of (**179**) showed a structure resembling benziodoxoles with an intramolecular distance of 2.707(5) Å between one of the sulfone oxygen atoms and the hypervalent iodine center [242]. The I-O bond length in the iodosyl group of (**179**) is 1.848(6) Å and the intramolecular O-I-O bond angle is 167.3(2)°. The iodine centers in (**179**) achieve a pseudo square-planar geometry by the formation of intermolecular I...O secondary bond (2.665(6) Å) to a neighboring iodosyl

oxygen atom [244]. Because of the excellent solubility in common organic solvents, compound (**179**) has powerful oxidizing properties. In particular, it reacts readily with tertiary phosphines and organic sulfides with the formation of the respective phosphine oxides and sulfoxides in high yield [245].

The same authors [245] have reported the preparation and X-ray structure of pseudo-benziodoxole (**180**) (Fig. 70), which can be used as a highly soluble nitrene precursor.

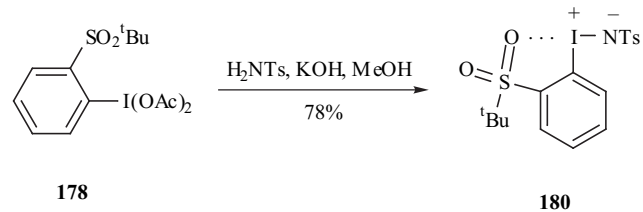


Fig. (70).

Imide (**180**) is readily soluble in organic solvents (up to 0.14 M in chloroform, which is a 50-fold increase over PhINTs) and can be analyzed by NMR in solution [245]. Single crystal X-ray analysis of (**180**) showed a structure of loosely associated centrosymmetric dimers with a long-range intramolecular I...N and I...O distance of more than 3.0 Å, quite unlike the infinite polymeric chains adopted in the solid state for PhINTs. One of the sulfonyl oxygen atoms forms a short intramolecular I...O secondary bond to the iodine atom with a bond length of 2.667 Å. Because of the excellent solubility in common organic solvents, compound (**180**) has high activity in the copper-catalyzed aziridination and sulfimidization reactions [245].

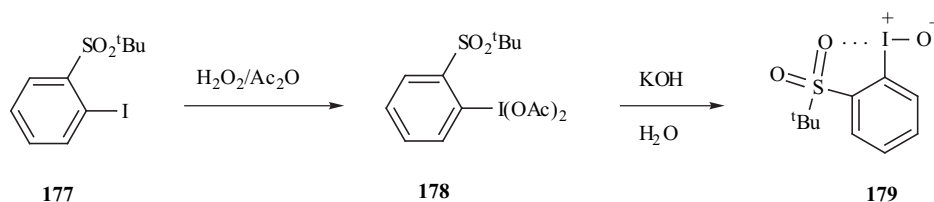


Fig. (69).

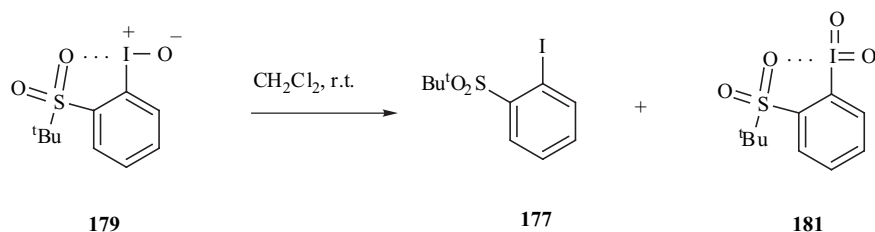
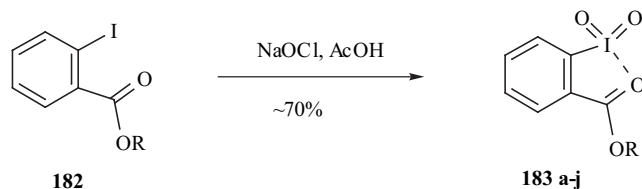


Fig. (71).

A new iodine(V) pseudo-benziodoxole (**181**) was prepared by the disproportionation of iodosylarene (**179**) (Fig. 71) [244]. The X-ray structure of product (**181**) shows a pseudo octahedral geometry with the I–O bond lengths in the iodyl group of 1.796 and 1.822 Å and an intramolecular distance of 2.693 Å between one of the sulfone oxygen atoms and the hypervalent iodine center [244].

Esters of 2-iodoxybenzoic acid (IBX–esters) (**183**), a new class of pentavalent iodine compounds with a pseudo-benziodoxole structure, can be conveniently prepared by hypochlorite oxidation of iodobenzoate esters (**182**) (Fig. 72) in the form of stable, white, microcrystalline solids [247]. This facile procedure allows for the preparation of reagents (**183**) derived from a wide variety of precursors, including primary, secondary, and tertiary alcohols, adamantanols, as well as optically active menthols and borneol. All products (**183**) have moderate to good solubility in common organic solvents, such as chloroform, dichloromethane, and acetonitrile. In CH_2Cl_2 , for example, the solubilities of (**183c**), (**183d**) and (**183e**) are 2.9, 0.2, and 1.7 M, respectively [247].



a: R = Me; **b:** R = Et; **c:** R = *i*-Pr; **d:** R = *tert*-Bu;
e: R = (–)-menthyl; **f:** R = (+)-menthyl; **g:** R = (±)-menthyl;
h: R = [(1*S*)-*endo*](–)-bornyl; **i:** R = 2-adamantyl; **j:** R = 1-adamantyl

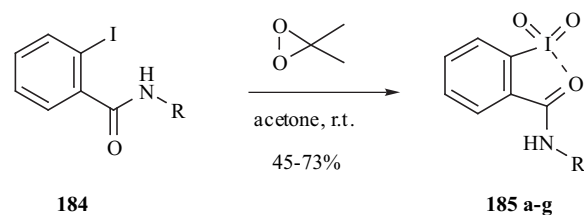
Fig. (72).

Structures of compounds (**183a**), (**183c**) and (**183d**) were established by single crystal X-ray analysis. In particular, the structure of (**183c**) shows a unit cell consisting of two crystallographically independent molecules. Strong secondary I•••O bonding interactions between neighboring molecules affords dimeric pairs, which are then linked together by a combination of strong and weak interactions, forming a polymeric motif. Within each molecule, an intramolecular close contact of 2.697 Å between the iodine(V) center and the oxygen atom of the ester group affords the pseudo-benziodoxole ring [247].

A range of alcohols can be oxidized by reagents (**183**) to the respective carbonyl compounds under mild conditions. For example, oxidation of benzyl alcohol in the presence of KBr in chloroform at 50 °C cleanly gives benzaldehyde as the only product detected by ^1H NMR spectroscopy. A variety of secondary alcohols, such as cyclohexanol and

cycloheptanol, are converted to the corresponding ketones in 95–98% yields [247].

The novel 2-iodoxybenzamides (IBX-amides) (**185**), which are stable and soluble compounds with unique and synthetically valuable oxidizing properties, can be prepared by the dioxirane oxidation of the readily available 2-iodobenzamides (**184**) (Fig 73) [248]. This procedure allows for the preparation of products (**185**) derived from numerous types of amino compounds, such as esters of natural α -amino acids (**185a,c–d**), an unnatural amino acid (**185b**), β -amino acids (**185e,f**), and (*R*)-1-phenylethylamine (**185g**). X-Ray data on (**185c**) reveals a pseudo-benziodoxole structure in which the intramolecular I•••O secondary bonds (2.594 Å) partially replace the intermolecular I•••O secondary bonds responsible for the polymeric structure of PhIO_2 and other previously reported iodylarenes. This structural characteristic substantially increases solubility and stability of these compounds in comparison to other I(V) reagents.



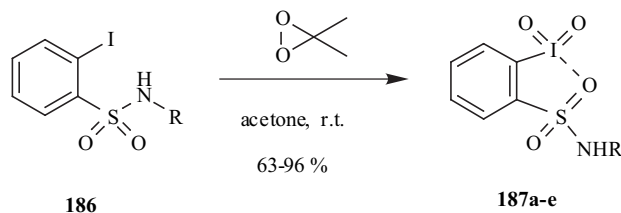
a: R = (*S*)-CH(CH₃)CO₂CH₃; **b:** R = (*R*)-CH(CH₃)CO₂CH₃;
c: R = (*S*)-CH(CH₂Ph)CO₂CH₃; **d:** R = (*S*)-CH(*i*-Bu)CO₂CH₃;
e: R = CH₂CH₂CO₂H; **f:** R = CH(CH₃)CH₂CO₂H; **g:** R = (*R*)-CH(Ph)CH₃

Fig. (73).

2-Iodoxybenzamides (**185**) are useful oxidizing reagents towards alcohols with a reactivity pattern similar to IBX. A wide range of alcohols can be oxidized by these reagents to the respective carbonyl compounds under mild conditions in chloroform. For example, benzyl alcohol cleanly gives benzaldehyde as the only product detected by ^1H NMR spectroscopy. A variety of secondary alcohols are effectively converted to the corresponding ketones in good yields using any of the reagents (**185a–c**), although reaction times vary as a function of the reagent used. Oxidative kinetic resolution of racemic *sec*-phenethyl alcohol using reagents (**185**) has also been investigated. In particular, the reaction of (**185c**) showed a very modest 9% ee. In contrast to DMP, reaction of reagent (**185b**) with *cis*-hexanediol effects oxidative cleavage to give hexanedial in 30% yield. It should be emphasized that iodylbenzene, PhIO_2 , as well as other non-cyclic iodylarenes, do not react with alcohols in the absence of acidic catalysis. In agreement with their structural features, the oxidizing reactivity of 2-iodoxybenzamides

(185) is closer to the benziodoxole-based pentavalent iodine reagents, in contrast to the non-cyclic iodylarenes [248].

Amides of 2-iodoxybenzenesulfonic acid (187) were recently prepared by the dioxirane oxidation of the corresponding 2-iodobenzenesulfamides and isolated as stable, microcrystalline products ((Fig 74) [251].



a: R = (S)-CH(CH₃)CO₂CH₃; b: R = (S)-CH(CH₂Ph)CO₂CH₃;
 c: R = (S)-CH(i-Pr)CO₂CH₃; d: R = (S)-CH(i-Bu)CO₂CH₃;
 e: R = (R)-CH(Ph)CH₃

Fig. (74).

These newest representatives of the pseudocyclic hypervalent iodine compounds can selectively oxidize benzyl alcohols to aldehydes [251].

4. CONCLUSIONS

The preceding survey of the chemistry of benziodoxole-based hypervalent iodine reagents reflects an active current interest in this highly versatile class of valuable reagents. The five-membered hypervalent iodine heterocycles derived from benziodoxole and benziodazole oxide have recently emerged as reagents of choice for various synthetically useful oxidative transformations. In particular, IBX and DMP and their analogs are widely used for the selective oxidation of primary and secondary alcohols and for a variety of other important oxidations. This surging interest in benziodoxoles is mainly due to the very useful oxidizing properties of these reagents, combined with their benign environmental character and commercial availability. We hope and anticipate that this review will stimulate further development of the chemistry and synthetic applications of hypervalent iodine reagents.

5. ACKNOWLEDGEMENTS

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