Reactions of IBX

New Reactions of IBX: Oxidation of Nitrogen- and Sulfur-Containing Substrates To Afford Useful Synthetic Intermediates**

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Despite its early description (1893),[1] *o*-iodoxybenzoic acid (**1**, IBX) languished, essentially forgotten, until the 1980s when the seminal works of Dess and Martin initiated a renaissance in interest in the chemistry of hypervalent iodine(v) reagents.[2] Within the past decade, the use of IBX as a reagent has grown dramatically, a surge driven by an improved method for its synthesis,[3] and by explorations into its chemistry that have unveiled its versatility in mediating a wide array of transformations with far-reaching synthetic applicability.[4] In particular, investigations from our own laboratories have revealed that IBX is a powerful single-electron-transfer (SET) agent that readily accepts new heteroatom-based ligands and, thus, can 1) effect the oxidation of ketones, aldehydes, and silyl enol ethers to the corresponding α,β-unsaturated carbonyl compounds,[5–7] 2) oxidize benzylic positions,[5] and 3) facilitate the cyclization of *N*-aryl amides, (thio)carbamates, and ureas to afford

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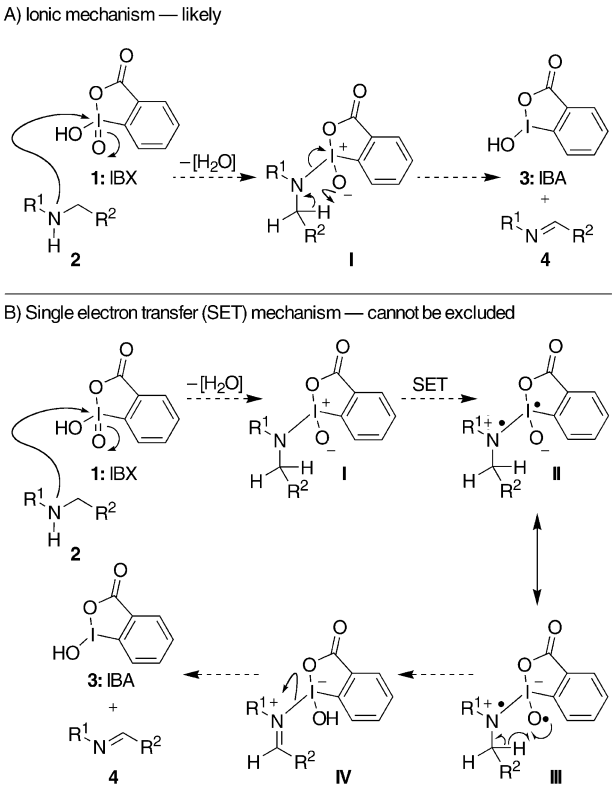
various heterocycles and amino sugars.[8–11] These developments prompted us to further postulate that reactions with other heteroatom-containing compounds might be feasible. For example, we rationalized, through the mechanism delineated in Scheme 1, that it might be possible to employ

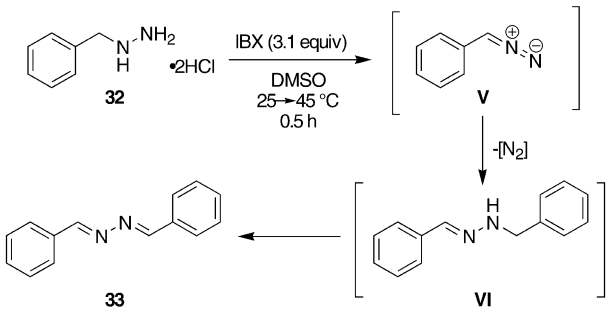


Scheme 1. Proposed A) ionic and B) single-electron-transfer (SET) mechanisms for the oxidation of amines to imines mediated by IBX (**1**). IBA = iodosobenzoic acid.

this reagent to oxidize unhindered amines to their imine counterparts. Herein, we report the successful direct oxidation of multifarious amines to the corresponding imines and oximes by IBX under mild conditions and in excellent yields, as well as a series of related transformations, including new entries into certain aromatic heterocycles, and the deprotection of dithianes to yield the corresponding carbonyl compounds.

Imines and oximes are ubiquitous and useful intermediates within the domain of synthesis, acting as electrophilic participants in a plethora of reactions including alkylations, condensations, or aza-Diels–Alder and other cycloadditions. A series of diverse protocols describing the oxidation of a limited range of amines to the corresponding imines have already been reported in the literature,[12–23] emphasizing synthetic interest in this transformation. The disparate nature of these procedures and the narrow range of amine substrates utilized, however, also serve to accentuate the shortcomings associated with each of these methods.[24]

In this context we were, therefore, gratified to observe, as we proceeded to investigate the potential of IBX in this transformation, that a diverse range of amine substrates could be smoothly and rapidly oxidized in excellent yield and under mild conditions as shown in Table 1. The inclusion of a cyanide, a halide, an *O*-benzyl group, or even a primary hydroxy group did not hinder the desired reaction (Table 1, entries 2, 5, 6, and 9). Among these examples, entry 5 is particularly remarkable, as IBX is perhaps best known as a mild and rapid oxidant for the conversion of alcohols into the corresponding carbonyl compounds[3] (see below), yet in this instance the primary hydroxy group remained unaltered over the course of the reaction (**14**→**15**). Interestingly, hydroxylamine **26** and hydroxylamine ether **28** were rapidly transformed into the oxime **27** and oxime ether **29**, respectively, in excellent yields under very mild conditions (Table 1, entries 12 and 13). The high yields observed in these reactions are notable because IBX has been reported to facilitate the rapid cleavage of various oximes to afford the corresponding carbonyl-containing compounds at room temperature.[25] When a hydrazine, such as **32**, rather than an hydroxylamine, was employed, oxidation with IBX was accompanied by concomitant dimerization and gas evolution (Table 1, entry 15). It is presumed that this dimerization proceeds through initial double oxidation to afford diazo intermediate **V**, followed by loss of nitrogen and insertion of the resultant carbene into the terminal N–H bond of a second molecule of **32**, perhaps organized by precoordination of several N-based ligands around an iodine center. The product **33** may then be obtained after a final IBX-mediated oxidation of the hydrazone **VI** (Scheme 2).

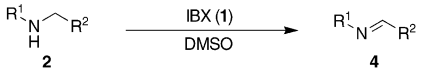


Scheme 2. Proposed mechanism for the IBX-induced conversion of hydrazine derivative **32** into dimeric product **33**. DMSO = dimethyl sulfoxide.

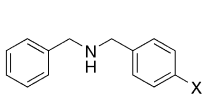
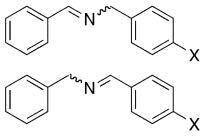
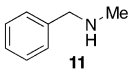
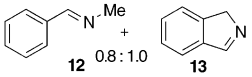
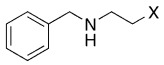
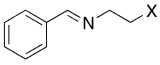
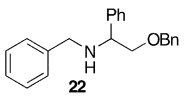
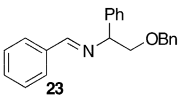
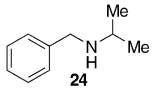
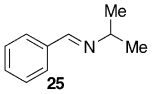
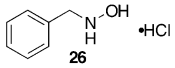
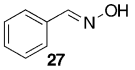
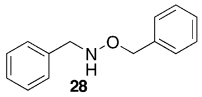
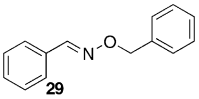
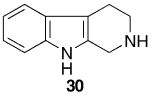
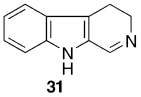
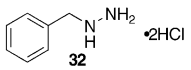
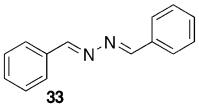
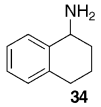
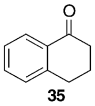
When a primary amine (**34**) was subjected to this procedure, the resultant imine could not be isolated as it was apparently hydrolyzed in situ to afford the corresponding ketone **35** directly (Table 1, entry 16). In substrate **18**, the secondary activated amine reacted rapidly, whereas the tertiary amine moiety remained unaltered over the course of the reaction (Table 1, entry 8). In general, this useful transformation does not necessarily require the elevated temperature (45 °C) used in the standard protocol. High yields can also be obtained when the reaction is conducted at room temperature (Table 1, entry 7); inevitably, however, significantly longer reaction times are required.

The observed transformations were, for the most part, regioselective when unsymmetrical secondary amines were

Table 1: Oxidation of amines with IBX. Synthesis of substituted imines, oximes, azines, and ketones.[a]



2 **4**

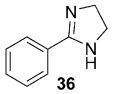
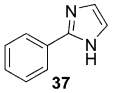
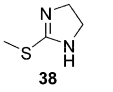
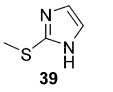
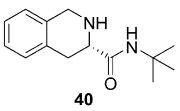
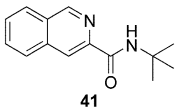
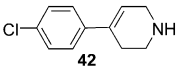
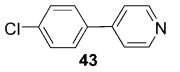
Entry	Starting material	Product(s)	*t* [h]	*T* [°C]	Yield [%]
					
1	**5**: X = H	**6**: X = H	0.5	45	83
2	**7**: X = Br	**8**: X = Br[b]	0.5	45	91
3	**9**: X = OMe	**10**: X = OMe[b]	0.5	45	95
4	 **11**	 **12** 0.8 : 1.0 **13**	0.5	45	70
					
5	**14**: X = OH	**15**: X = OH	0.5	45	79
6	**16**: X = OBn	**17**: X = OBn	0.5	45	89
7	**16**: X = OBn	**17**: X = OBn	9	25	81
8	**18**: X = NMe_2	**19**: X = NMe_2	0.5	45	77
9	**20**: X = CN	**21**: X = CN	0.5	45	89
10	 **22**	 **23**	14	45	49[c]
11	 **24**	 **25**	1	45	88
12	 **26**	 **27**	0.5	45	97
13	 **28**	 **29**	0.5	45	98
14	 **30**	 **31**	0.5	45	98
15	 **32**	 **33**	0.5	45	94
16	 **34**	 **35**	40	25	79

[a] Reactions were conducted on a 0.2–0.5-mmol scale in DMSO with 1.1 equivalents of IBX. [b] Mixture of isomers observed by ^{1}H NMR spectroscopy. [c] Unreacted starting material was also recovered (37%).

employed. Generally, the reaction proceeded to form the conjugated *N*-benzylidene preferentially rather than occurring at the alternative unactivated site to furnish the imine (Table 1, entries 5–9, 11, and 14). This finding contrasts with previous protocols, which were not as discriminating and thus afforded regioisomeric mixtures.[15] (Activation of the methylene to be oxidized is not, however, a prerequisite: see Table 1, entry 4 and Table 2, entries 1 and 2). There are two exceptions to this observation of regioselectivity: The first instance is when differentiation is exhibited by remote substitution on one of the two phenyl rings of an *N*-dibenzylamine. In examples of this case, the relative rates conspired to afford a mixture of regioisomers in the imine product (Table 1, entries 2 and 3), despite the electronic differences in the aromatic rings derived from substitution with bromide or methoxy groups. The second example in which a lack of regioselectivity is observed involved *N*-benzylmethylamine (**11**), which upon treatment with IBX, gave a mixture of products (**12**/**13** ≈ 0.8:1.0; Table 1, entry 4). Imine **12** arises from simple oxidation at the benzylic position of the starting material **11**, whereas the formation of its partner, **13**, is initiated when oxidation of the methyl group is followed by cyclization of the so-formed electrophile onto the proximal aromatic ring, and concludes with a final benzylic oxidation. This transformation, if adopted, holds promise for the synthesis of isoquinolines and other heterocycles.

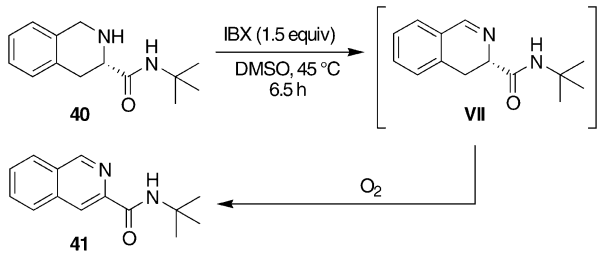
The abundance of aromatic heterocycles in nature and their prominence in medicinal chemistry inspired us to consider using IBX-mediated oxidation of nitrogen-containing cyclic compounds as a means to access such systems. The concept was initially examined by treating imidazoline **36** (Table 2) with IBX (1.5 equiv) in DMSO for 14 h at 45 °C. Despite requiring oxidation at an unactivated α-methylene group with respect to the nitrogen atom (i.e. not a benzylic methylene; compare with examples in Table 1), the reaction proceeded smoothly to furnish the corresponding imidazole (**37**) in high yield (Table 2, entry 1). Likewise, 2-methylsulfanylimidazoline (**38**) was transformed into the corresponding 2-methylsulfanylimidazole (**39**) in excellent yield (Table 2, entry 2), suggesting that the presence of a sulfur substituent is not necessarily detrimental to the success of the reaction (see below). Isoquinoline **41** and pyridine **43** could also be obtained from terahydroisoquinoline **40** and tetrahydropyridyl compound **42**, respectively (Table 2, entries 3 and 4). In these examples, it is presumed that the initial IBX-mediated oxidation step is followed by rapid aerobic autoxidation (IBA-mediated oxi-

Table 2: Synthesis of substituted imidazoles, isoquinolines, and pyridines from precursor cyclic amines mediated by IBX (**1**).[a]

Entry	Starting material	Product	*t* [h]	Yield [%][b]
1	 **36**	 **37**	14	71
2	 **38**	 **39**	16	81
3	 **40**	 **41**	6.5	95
4	 **42**	 **43**	48	76

[a] Reactions were conducted on a 0.3–0.5-mmol scale in DMSO with 1.5 equivalents of IBX at 45 °C. [b] Yield of isolated product, with no purification required.

dation cannot be excluded), as less than 2 equivalents of IBX were employed in both cases and the sole product was the fully aromatized heterocycle (Scheme 3). The proposed aerial oxidation is in line with precedent set by a similar observation

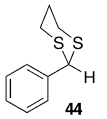
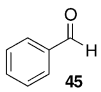
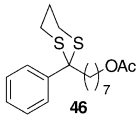
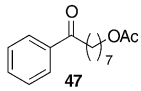
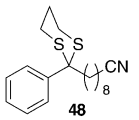
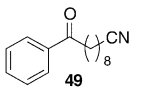
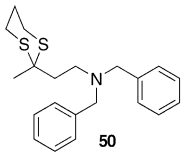
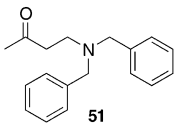
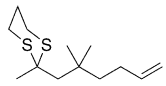
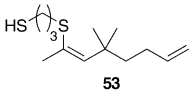
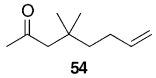


Scheme 3. Aromatization of tetrahydroisoquinoline substrate **40** through initial IBX-mediated oxidation followed by (presumed) autoxidation to afford isoquinoline **41**.

in analogous compounds.[21] It is of interest to contrast these last two examples with the oxidation of **30** (Table 1, entry 14) in which no products derived from a second oxidation were observed.

With the knowledge acquired from these investigations and previous reports[4] describing the behavior of IBX in reactions in which the presence of oxygen and nitrogen is crucial, it now seemed prudent to evaluate the reactivity of some common sulfur-containing substrates in order to obtain a fuller understanding of the reactivity profile of this reagent. To this end, it should be noted that iodine has, for some time, been known to be thiophilic, a feature that has previously been exploited in a number of protocols for the deprotection of dithianes.[26–28] Indeed, the hypervalent iodine(III) reagent, bis(trifluoroacetoxy)iodobenzene, may be employed for the rapid removal of dithiane protecting groups to generate the corresponding carbonyl group (or furnish directly the *O*-acetal/ketal counterpart), albeit under relatively acidic conditions. Initially, the dithiane derivative of benzaldehyde **44** was treated with IBX in wet DMSO to evaluate whether IBX would offer a milder alternative to bis(trifluoroacetoxy)iodobenzene (Table 3, entry 1). Rapid dithiane cleavage was followed by isolation of benzaldehyde (**45**) in essentially quantitative yield after a simple workup procedure. Similar

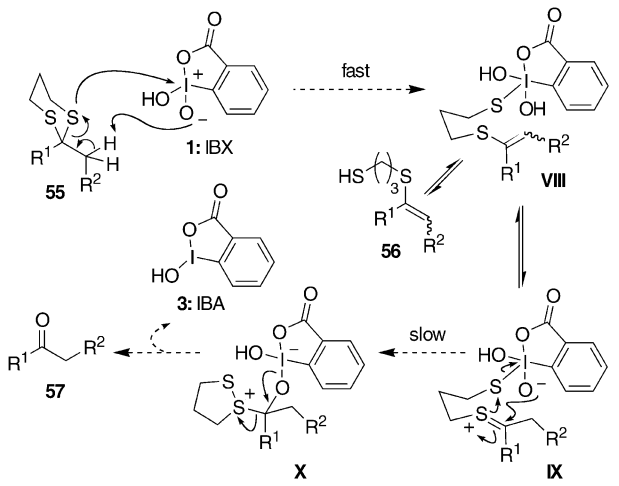
Table 3: IBX-induced cleavage of dithianes to the corresponding carbonyl compounds.[a]

Entry	Starting material	Product	*t* [h]	Yield [%][b]
1	 **44**	 **45**	0.3	99
2	 **46**	 **47**	1	95[c]
3	 **48**	 **49**	1	98[c]
4	 **50**	 **51**	6	96[c]
5	 **52**	 **53**	0.1	98
6		 **54**	6	96[c]

[a] Reactions were carried out on 0.1–1.0 mmol scale in H_2O:DMSO (1:9) with 2.0 equiv of IBX at 25 °C. [b] Isolated yield with no purification required. [c] 1–10 mol% AcOH added.

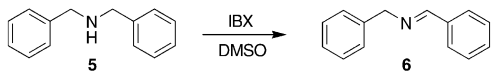
facile deprotections were carried out with a number of other benzylic dithianes (Table 3, entries 2 and 3), including a substrate bearing a tertiary amine substituent (Table 3, entry 4), a function that is known to retard the IBX-mediated oxidations of alcohols (see below).[6,29] Interestingly, when alkyl dithiane **52** (Table 3, entry 5) was subjected to the new protocol, the intermediate compound **53** could be isolated after a short reaction time, giving some insight into the mechanism of this cleavage process (Scheme 4). When **53** was resubjected to the reaction conditions, the parent ketone **54** was isolated in high yield (Table 3, entry 6).

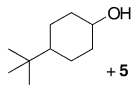
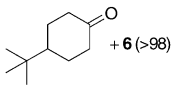
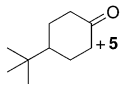
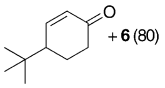
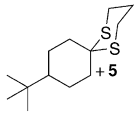
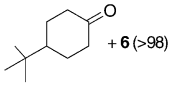
Having established the new IBX-mediated transformations reported above, it was now necessary to compare the relative rates of these reactions so that selectivity parameters could be secured. A series of competition experiments was, therefore, conducted (Table 4). Remarkably, in the presence of secondary alcohol **58**, saturated ketone **59**, or dithiane **60**,



Scheme 4. Postulated mechanistic rationale for the deprotection of dithianes by IBX under neutral conditions.

Table 4: Relative reactivity of IBX towards secondary amine **5** versus alcohol **58**, ketone **59**, and dithiane **60**.[a]



Entry	Starting materials[b]	Conditions	Conversion ([%])[c]
1	 **58** + **5**	IBX (1.5 equiv), DMSO	 + **6** (>98) (not observed)
2	 **59** + **5**	IBX (1.0 equiv), DMSO	 + **6** (80) (not observed)
3	 **60** + **5**	IBX (1.5 equiv), DMSO/CH_2Cl_2 (10:1)[d]	 + **6** (>98) (not observed)

[a] Reactions were carried out on a 0.2–0.5-mmol scale at 45 °C for 45 min. [b] 1 equivalent each of **5** and **58**, **59**, or **60** was used. [c] Determined by ^{1}H NMR spectroscopy. [d] Dichloromethane was added to improve substrate solubility.

the formation of imine **6** was convincingly favored in each case. In the case in which ketone α,β-unsaturation was evaluated in the presence of dibenzylamine **5** (Table 1, entry 2), *N*-benzylidene formation could not be driven to completion, as substrate degradation became a factor with increased amounts of IBX.

In conclusion, we have discovered a number of new reactions of IBX with heteroatom-containing substrates and demonstrated their utility in organic synthesis. Specifically, we have developed general IBX-induced procedures for the generation of imines from secondary amines under mild conditions and in notably high yields. Furthermore, the oxidative aromatization of nitrogen heterocycles from simple substrates, including those with no activating groups, has been realized. Finally, a new mild procedure for the cleavage of dithianes with IBX has been unveiled. Although these novel reactions induced by IBX are expected to find considerable applications in organic synthesis, new modes of reactivity for this rather old reagent are still anticipated.

Experimental Section

Typical oxidation procedure: IBX (1.0–1.5 equiv) was added to a solution of the amine substrate (1.0 mmol) dissolved in DMSO (2.5 mL, 0.4 M) at ambient temperature. The resulting mixture was heated (45 °C) and the reaction progress was monitored by ^{1}H NMR spectroscopy ([D_6]DMSO). Upon completion, the reaction mixture was diluted with saturated aqueous $Na_2S_2O_3$ (2.5 mL) and an equal volume of EtOAc. The suspension was stirred for about 5 min, and, if necessary, any remaining solids were filtered off through a pad of celite and washed with EtOAc (3 × 1 mL). The combined solution was basified with saturated aqueous $NaHCO_3$ (2.5 mL) and subsequently extracted with EtOAc (2 × 2.5 mL). The organic solution was then washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL). After drying ($MgSO_4$), the solvent was removed in vacuo to yield the crude product, which rarely required further purification.

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Keywords: imines · nitrogen heterocycles · oxidation · oximes · synthetic methods

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