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Published on Web 04/06/2004

o-Iodoxybenzoic Acid (IBX) as a Viable Reagent in the Manipulation of Nitrogen- and Sulfur-Containing Substrates: Scope, Generality, and Mechanism of IBX-Mediated Amine Oxidations and Dithiane Deprotections

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Abstract: *o*-Iodoxybenzoic acid (IBX), a highly versatile hypervalent iodine(V) reagent, was found to efficiently mediate the dehydrogenation of amines in addition to facilitating the oxidative cleavage of dithioacetals and dithioketals. Through the development of relevant IBX-based protocols, a plethora of useful synthetic intermediates, including imines, oximes, ketones, and aromatic *N*-heterocycles, were found to be readily accessible under notably mild conditions. Further investigation of these transformations led to the elucidation of valuable mechanistic details, resulting in the conclusion that they proceed via ionic rather than single electron transfer (SET) pathways.

Introduction

Ever since the innovative work by Dess and Martin, modern explorations into the chemistry of hypervalent iodine(V) compounds have rapidly become the subject of burgeoning interest. The discovery of the Dess−Martin periodinane (DMP), in particular, as a mild oxidant affecting the conversion of alcohols to their corresponding carbonyl compounds in 1983,[1] heralded the commencement of this resurgence, where repeated demonstrations attesting to the potent synthetic applicability of iodine(V) reagents have since been displayed.[2] More recently within the past decade, *o*-iodoxybenzoic acid (IBX),[3] the precursor of DMP, has seen a dramatic increase in use as a reagent, despite its first description having been published over a century ago (1893).[4]

Investigations from our own laboratories have revealed a series of new paradigms for iodine(V)-mediated reactions,[5−13] specifically highlighting IBX as a reagent capable of: (1) affecting the oxidation of benzylic sites,[5,6] (2) facilitating the cyclization of functionalized anilide systems to their heterocyclic counterparts,[7−10] and (3) dehydrogenating ketones, aldehydes, and silyl enol ethers to their corresponding α,β-unsaturated carbonyl compounds.[5,11−13] Perhaps the most significant insight garnered from these studies has been the realization that IBX can act as a single electron transfer (SET) agent,[5,8,10] demonstrating that oxidations employing this reagent are able to proceed via either radical or ionic pathways, as dictated by variables, including substrate characteristics and reaction conditions. The so-revealed unique mechanistic dichotomy is indicative of the reagent's versatility and broad potential in further systems.

In the context of this ongoing program, we sought to further elaborate on the developments discussed above by challenging the bounds of IBX-based synthetic technology through the evaluation of its reactivity toward previously unexplored classes of heteroatom-bearing substrates. In so doing, it was anticipated that an improved grasp of the chemistry of IBX could be established, along with a heightened awareness of the scope of transformations capable of being mediated by λ^5-iodanes. As such, we report herein the following advances in IBX-mediated chemistry: (1) accomplishment of the direct oxidation of primary and secondary amine compounds to furnish their respective imine, oxime, and hydrolyzed counterparts, (2) the

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(2) (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. In *Electronic Encyclopedia of Reagents for Organic Synthesis (e-EROS)*; Paquette, L. A., Ed.; Wiley-VCH: Weinheim, Germany, in press; see also references therein. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523.
(3) *Caution!* IBX should be treated as a shock- and temperature-sensitive high explosive, as well as an oxidizer. We thank Prof. Jeremiah P. Freeman, Department of Chemistry, 251 Nieuwland Science Hall, University of Notre Dame, Notre Dame, IN 46556-5670 for bringing this information to our attention.
(4) Hartman, C.; Meyer, V. *Ber. Dtsch. Ges.* **1893**, *26*, 1727.
(5) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.
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10.1021/ja0400382 CCC: $27.50

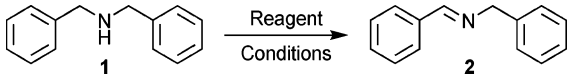
successful deprotection of dithioacetals and dithioketals to yield their parent carbonyl species, (3) the oxidative dimerization of hydrazines and hydrazones, via organized iodine coordination complexes, and (4) the synthesis of substituted imidazoles, pyridines, and pyrroles through the facile aromatization of *N*-heterocyclic precursors.

The pertinence of this methodology stems from the fact that all the aforementioned transformations are quite fundamental in nature and can be easily applied to a multitude of synthetic strategies. Aromatic nitrogen heterocycles have long been of widespread interest by virtue of their ubiquitous presence in multifarious natural products and other biologically active compounds. Furthermore, imines and dithianes have found, and will continue to find, extensive use in a myriad of synthetic contexts. With these applications in mind, the mild and chemoselective nature of IBX, coupled with the high reaction yields that frequently accompany its employment, has rendered this reagent as a unique and powerful tool in chemical synthesis.

Results and Discussion

1. Dehydrogenation of Amines Using IBX. Many protocols affecting the oxidation of amines to imines have been reported in the literature, with the multiplicity of these reports serving to emphasize the versatility of this transformation, but also concomitantly accentuating the shortcomings that accompany each of these methods.[14−24] The lack of a mild and general procedure for the oxidation of amines reflects a severe deficiency in the synthetic utility of such processes. This state of affairs is rather odd given the fact that such a method would present a facile route to common synthetic building blocks such as imines and oximes, thus providing a direct entryway into various heterocycles as well as to a plethora of transformations, including alkylations, aza-Diels−Alder cycloadditions, and condensation reactions.[25] Among the known procedures for this transformation, amine oxidation conducted with catalytic *tetra*-*N*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) as a stoichiometric co-oxidant, is notably uncomplicated and usually undertaken at room temperature. However, only a small number of benzylamines were examined under these conditions, and optimum yields were only obtained after up to 72 h of reaction time and increased equivalents of NMO.[14] Ruthenium catalysis was also utilized in a more recent procedure where oxygen serves as the stoichiometric co-oxidant in refluxing triflurotoluene.[15] Other transition-metal-based methods rely on copper(II) bromide-lithium *tert*-butoxide,[16] expensive cobalt Schiff base complexes,[17] manganese(III)/iron(III) porphyrins or manganese(III) salen,[18] or manganese dioxide (8 equiv) in refluxing benzene.[19] Reports of dehydrogenation accomplished with Fremy's salt[20] and diphenylselenium bis(trifluoroacetate)[21] are restricted to tetrahydroisoquinoline systems, and yet other procedures employing Swern conditions,[22] di-*tert*-butyliminoxyl radical,[23] iodosobenzene,[18] and alkylperoxy-λ^3-iodane[24] have similarly only been accomplished on a handful of simple substrates. In general, each method fails to present a broad scope by asserting its compatibility with a wide variety of systems. Thus, as we proceeded with our investigations into the chemistry of hypervalent iodine(V), it was gratifying to observe that an abundance of amine substrates were readily oxidized with IBX in excellent yield, under particularly mild conditions and with short reaction times.

Table 1. Discovery and Optimization of the Iodine(V)-Mediated Oxidation of Amines[a]



1 **2**

entry	reagent	conditions	yield[b]
1	IBX (1.1 equiv)	DMSO, 45 °C, 30 min	83
2	IBX (1.1 equiv)	DMSO, 25 °C, 10 min	83
3	IBX·MPO (1.1 equiv)	DMSO, 25 °C, 10 min	44[c]
4	DMP (1.1 equiv)	CH_2Cl_2, 25 °C, 10 min	64
5	I_2O_5 (1.1 equiv)	DMSO/H_2O (9:1), 25 °C, 1.5 h	1[c]
6	IBA (1.1 equiv)	DMSO (0.1 M), 25 °C, 2 h	3[c]

[a] Reactions were conducted on 0.2−0.3 mmol scale at a concentration of 0.3 M except where noted. [b] Isolated yield. In percent. [c] Unreacted starting material was also recovered (entry 3: 44%, entry 5: 98%, entry 6: 94%). IBX = *o*-iodoxybenzoic acid, MPO = 4-methoxypyridine *N*-oxide, IBA = *o*-iodosobenzoic acid, DMSO = dimethyl sulfoxide.

As shown in Table 1, entry 2, the oxidation of dibenzylamine (**1**) to its benzylidene counterpart (**2**) was performed smoothly upon treatment with IBX at room temperature for 10 min. These conditions were instituted following the communication of our initial results in this area,[26] as a result of the discovery that many amine oxidations conducted with IBX do not need the elevated temperatures and longer reaction times previously employed for this transformation (entry 1, Table 1). In the process of developing this hypervalent iodine-mediated reaction, a number of additional iodine(V) reagents were also examined. Like IBX, DMP was discovered to be a viable amine oxidant (entry 4, Table 1), although the yield of imine **2** was considerably lower, presumably due to the acidic nature of the reaction media. Dehydrogenation of **1** proved to be somewhat sluggish when subjected to IBX·MPO complex (entry 3, Table 1), first employed in the context of aldehyde and ketone dehydrogenation,[12] and virtually nonexistent when diiodine pentoxide (I_2O_5) was utilized (entry 5, Table 1). The iodine(III) compound *o*-iodosobenzoic acid (IBA) was also examined (entry 6, Table 1) to assert that the observed conversion of **1** to **2** in entries 1 and 2 was occurring as a result of the action of IBX, without contribution from its byproduct IBA.

As shown in Table 2, the IBX dehydrogenation protocol tolerates a wide range of substrate functionality, and furthermore, has shown to affect the oxidation of secondary amines rapidly and frequently in excellent yield. In particular, substrates with nitrogen-containing components, aside from a secondary amine, all furnished the desired imines in high yield (entries 6, 7, and 12, Table 2). Likewise, a halide, benzyl ether, and even a primary hydroxy group were subjected to the established reaction conditions and found to be unaffected, further signifying

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(22) Keirs, D.; Overton, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1660.
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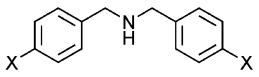
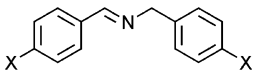
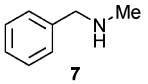
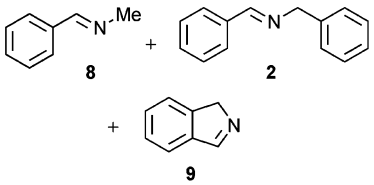
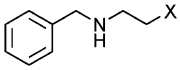
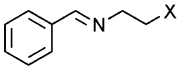
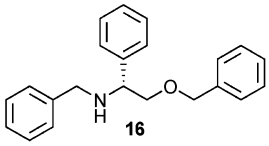
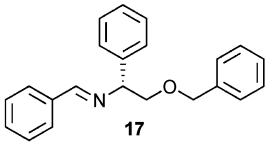
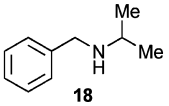
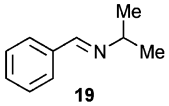
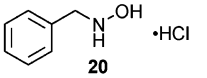
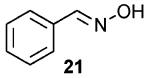
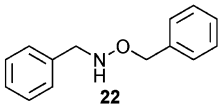
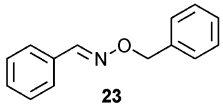
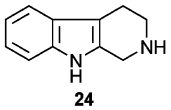
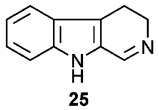
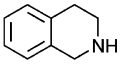
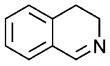
(25) Bailey, P. D.; Morgan, K. M. *Organonitrogen Chemistry*; Oxford University Press: New York, 1996.
(26) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077.

Table 2. Oxidation of Secondary Amines with IBX: Synthesis of Substituted Imines and Oximes[a]

Entry	Substrate	Product(s)	*t* (min)	Temp (°C)	Yield (%)[b]
					
1	**3:** X = Br	**4:** X = Br	10	25	91
2	**5:** X = OMe	**6:** X = OMe	20	45	99
3	**5:** X = OMe	**6:** X = OMe	10	25	61[c]
4	 **7**	 **8** **2** **9**	10	25	72[d]
					
5	**10:** X = OH	**11:** X = OH	20	45	79
6	**12:** X = NMe_2	**13:** X = NMe_2	10	25	74
7	**14:** X = CN	**15:** X = CN	10	25	95
8	 **16**	 **17**	840	45	78[e]
9	 **18**	 **19**	60	45	88
10	 **20**	 **21**	10	25	96
11	 **22**	 **23**	10	25	99
12	 **24**	 **25**	20	25	99[f]
13	 **26**	 **27**	10	25	78[g]

[a] Reactions were conducted on 0.2−0.5 mmol scale in DMSO with 1.1 equiv of IBX except where noted. [b] Isolated yield with no chromatography necessary. Much of the unaccounted material is presumed to be imine hydrolysis product. [c] Based on recovered starting material (31% product, 49% recovered **5**, 20% *p*-methoxybenzaldehyde). [d] Product ratio of **8**:**2**:**9** observed to be 0.8:1.0:trace by ^{1}H NMR spectroscopy. [e] Based on recovered starting material (49% product, 37% recovered **16**). [f] Based on recovered starting material (40% product, 59% recovered **24**). [g] 1.0 equiv of IBX was employed.

the chemoselectivity of IBX (entries 1, 8, and 5, Table 2). The propensity for IBX to selectively act on a secondary amine moiety, even in the presence of a primary alcohol, is truly remarkable, as IBX is well-established as a very effective and mild oxidant for alcohols.[27] Other intriguing examples from Table 2 include entries 10 and 11, where hydroxylamines **20** and **22** were seamlessly converted to the corresponding oxime (**21**) and oxime ether (**23**) in high yield, despite IBX being reported to facilitate the hydrolysis of oximes to their respective carbonyl compounds.[28] Also of note is entry 4, where the subjection of *N*-methylbenzylamine to IBX surprisingly revealed *N*-benzylidenebenzylamine (**2**) as the major product, in addition to the anticipated *N*-benzylidenemethylamine (**8**). It is proposed that this outcome resulted from the existence of a hydrolysis/cross-condensation pathway following the initial oxidation of

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(28) Bose, D. S.; Srinivas, P. *Synlett* **1998**, 977.

Scheme 1. Proposed Mechanism Leading to the Formation of **2**, **8**, and **9** from Precursor Secondary Amine **7**

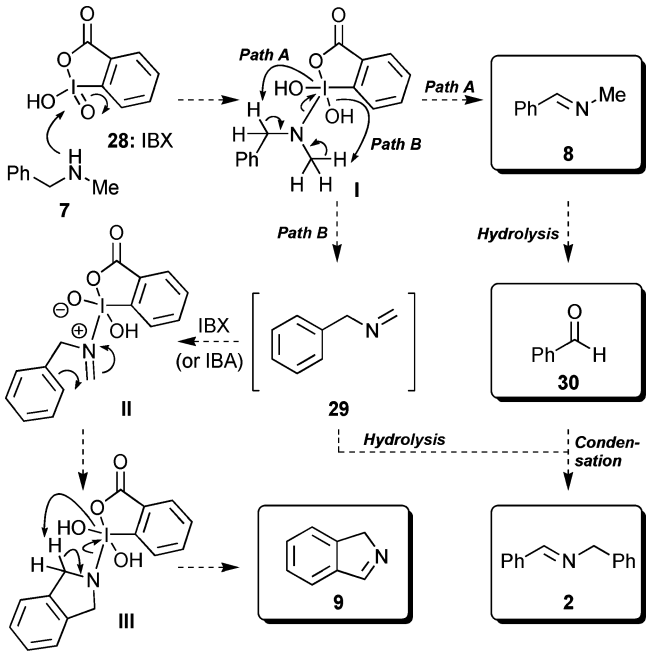
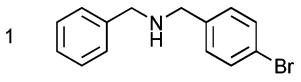
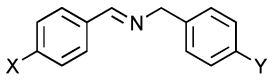
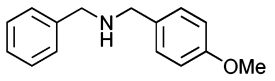
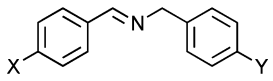


Table 3. Oxidation of Unsymmetric Dibenzylamines **31** and **34** in Support of an in Situ Hydrolysis/Cross-Condensation Pathway[a]

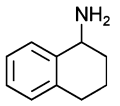
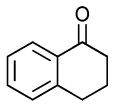
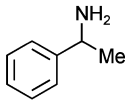
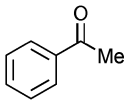
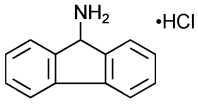
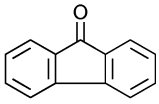
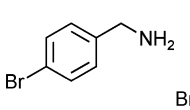
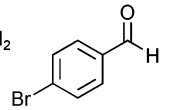
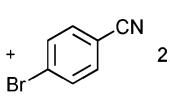
Entry	Substrate	Products (ratio[b])	Yield (%)[c]
1	 **31**	 **2:** X = Y = H (1.0) **32:** X = H, Y = Br (0.8) **33:** X = Br, Y = H (1.7) **4:** X = Y = Br (1.2)	99
2	 **34**	 **2:** X = Y = H (1.0) **35:** X = H, Y = OMe (1.6) **36:** X = OMe, Y = H (0.7) **6:** X = Y = OMe (1.0)	99

[a] Reactions were conducted on 0.2−0.5 mmol scale in DMSO (45 °C) for 30 min with 1.1 equiv of IBX. [b] Ratio of products determined by ^{1}H NMR spectroscopy. [c] Isolated yield with no chromatography necessary.

either the *N*-benzyl or *N*-methyl group as depicted in Scheme 1. Evidence for the formation of isoindole (**9**) was also obtained (HRMS), suggesting the possibility of an additional pathway consisting of a Mannich-type cyclization, followed by subsequent benzylic oxidation from the unobserved intermediate **29** (Scheme 1).

To confirm the presence of imine hydrolysis and consequent cross-condensation in cases involving the dehydrogenation of asymmetric substrates, compounds **31** and **34** (Table 3) were synthesized and subjected to the standard reaction conditions based on the hypothesis that IBX would be able to oxidize either benzylic position and, hence, provide the opportunity for compound scrambling. As expected, treatment of dibenzylamines **31** and **34** with IBX resulted in the formation of four distinct imine products as presented in Table 3, proving the labile nature of the benzylidene moiety when exposed to the standard

Table 4. Oxidation of Primary Amines with IBX[a]

Entry	Substrate	Product(s)	IBX (eq)	*t* (h)	Yield (%)[b]
1	 **37**	 **38**	1.1	48	79
2	 **39**	 **40**	1.1	51	94
3	 **41**	 **42**	2.0	5	99
4	 **43**	 **44** +  **45**	2.5	0.2	99[c]

[a] Reactions were conducted on 0.2−0.8 mmol scale in DMSO at 25 °C. [b] Isolated yield with no chromatography necessary. [c] Ratio of **44** to **45** determined to be 1.0:3.3 by ^{1}H NMR spectroscopy.

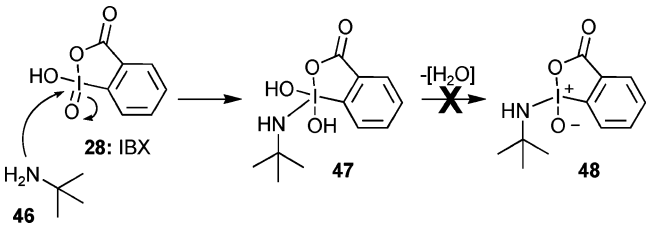
conditions of this protocol. These results also lend credence to the proposed mechanism as displayed in Scheme 1.

Aside from demonstrating considerable tolerance, IBX has proven its ability to cleanly oxidize specific substrates where other reported means have failed. For example, *N*-benzylisopropylamine (**18**) was cleanly converted to *N*-benzylideneisopropylamine (**19**) (entry 9, Table 2), where comparable reaction with manganese dioxide generated no well-defined products.[19] In addition, IBX generally shows a clear preference for the activation of benzylic sites, in contrast with other methods that have been revealed to be less discriminating.[16] To illustrate this point, when asymmetric amine substrates were subjected to IBX (entries 5−7, 9, 12, and 13, Table 2), dehydrogenation proceeded in admirable yield to the conjugated imines. An exception to this pattern is seen in the case of compound **7** (vide supra).

Following the successful implementation of IBX-induced oxidation on a host of secondary amines, we sought to match these observations with a range of primary amines. However, when primary amines were subjected to IBX, the isolation of pure imine proved difficult as the reaction conditions conspired to afford mixtures of the desired oxidation products and the corresponding hydrolyzed products even with the application of short reaction times. Therefore, the resultant carbonyl species was isolated in most cases, presumably due to hydrolysis of the initially formed imine product in situ (Table 4). The anomaly within Table 4 is entry 4, where not only was the predicted aldehyde obtained, but the nitrile **45** was also observed as the major product. The cyanide must result from the further dehydrogenation of the corresponding intermediate imine, where, in the case of substrate **43**, a second α-amino hydrogen is available.

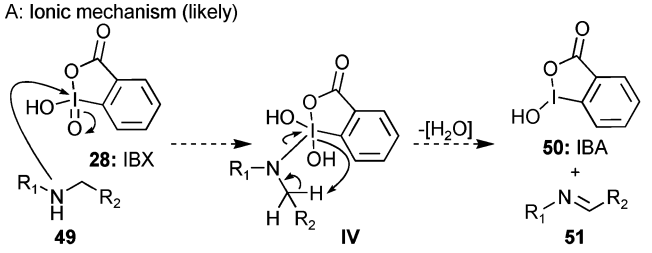
In an effort to probe the mechanistic detail of the transformations discussed above (Tables 1−4), we first asked the question: does the first step involving the association of a given nitrogen-based ligand with IBX serve merely as a fleeting

Scheme 2. Observation of a Stable IBX−Amine Complex (**47**)

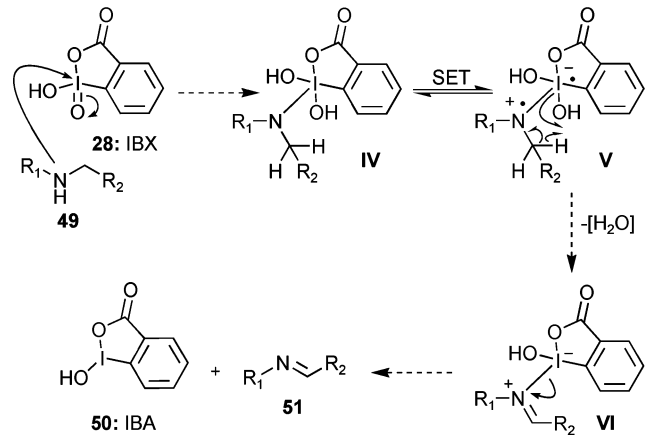


Scheme 3. Proposed (A) Ionic and (B) Single Electron Transfer (SET) Mechanisms for the Oxidation of Amines Mediated by IBX

A: Ionic mechanism (likely)



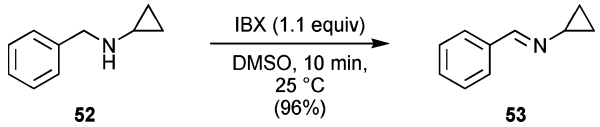
B: Single electron transfer (SET) mechanism (cannot be excluded)



prelude to loss of water, or is the intermediate iodine(V) species favored until a later stage, where imine generation and release of water could conceivably take place in a concerted fashion? To probe this matter, it was presumed that an amine substrate containing no abstractable α-amino hydrogen atoms would form a stable complex with IBX, but would be barred from engaging in amine oxidation and could, therefore, be detected as either the iodine(V) species, generated on association, or the ligand-exchange species, resulting from subsequent loss of water (Scheme 2). Hence, *tert*-butylamine (**46**) and IBX (**28**) were stirred together at room temperature for 48 h in DMSO, and upon examination by ESI-MS and ^{1}H NMR, the iodine(V) compound (**47**) was observed, with no evidence for **48**. This result is valuable, as it intimates that a compound analogous to **47**, not **48**, represents a local energy minimum along the typical reaction course.

We have postulated, on the basis of the mechanistic insights of relevant iodine(V) oxidation chemistry,[5,8,10] that after association of the amine substrate with IBX, as discussed previously, reduction at the iodine center could then either proceed via an ionic, concerted pathway as shown in Scheme 3 (alluded to in Scheme 1) or by an ensuing SET to afford a nitrogen radical cation (**V**), followed by fragmentation. Both of these processes consequently supply the desired imine moiety along with *o*-iodosobenzoic acid (IBA). In attempting to gain

Scheme 4. Reaction of *N*-Benzylcyclopropylamine (**52**) with IBX Leads to Formation of Benzylidene Product **53**



information as to whether amine oxidations mediated by IBX proceed via an ionic or SET mechanism, substrate **52** was synthesized (Scheme 4). The built-in cyclopropyl group was anticipated to act as an intramolecular radical trap and offer relevant insight regarding the presence of a nitrogen radical cation. Aminocyclopropanes have been reported to undergo radical-based fragmentation after one-electron oxidation[29] and, as such, have been previously instituted to establish the role of nitrogen radical cations in the mechanistic pathways of cytochrome P-450 and monoamine oxidase.[30] Reports, however, have focused primarily on tertiary amines, presumably due to the difficulty in promoting electron transfer in secondary and primary amines, which lack electron-donating inductive substituents.[31] Along these lines, treatment of **52** with IBX, as shown in Scheme 4, led to the facile formation of **53**, with the adjacent cyclopropyl group left intact. This observation may support the occurrence of an ionic pathway, although the possibility of process B shown in Scheme 3 cannot be completely excluded.

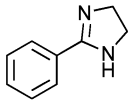
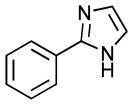
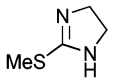
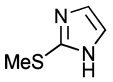
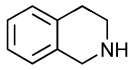
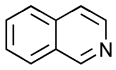
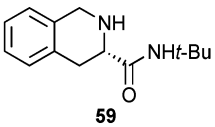
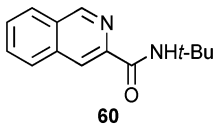
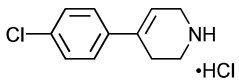
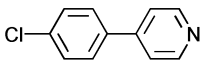
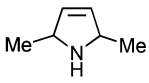
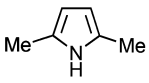
2. Aromatization of Functionalized *N*-Heterocycles with IBX. Methods for forming aromatic nitrogen heterocycles are presently of considerable interest, as such motifs are expressed in an abundance of biologically active natural products as well as in many of the synthetic lead compounds employed within the field of medicinal chemistry.[32] Therefore, a novel means to access such compounds by way of IBX could, potentially, impart a valuable contribution to such synthetic efforts.

As such, when IBX-mediated chemistry was extended to include a variety of cyclic amine substrates, a dichotomy was observed where anticipated dehydrogenation at the activated position occurred in some cases (e.g., entries 12 and 13, Table 2), while further oxidation was evidenced in others (e.g., entries 3−5, Table 5). This aromatization, in the cases of entries 4 and 5 (Table 5), is thought to be induced by rapid autoxidation following an initial IBX-mediated oxidation to the conjugated imine species, as conversion to the fully aromatic **60** and **62** was discerned with less than 2 equiv of IBX with no evidence of partially oxidized products (Scheme 5). This proposal is supported by literature precedent, wherein similar observations were made in the oxidation of analogous systems.[21] However, in the case of substrate **26**, it was established that conditions could be orchestrated to provide either **27** or the fully aromatic system **58**, suggesting that the second oxidation, in this context, is likely an IBX-dependent process (entry 13, Table 2; entry 3, Table 5).

This aromatization chemistry was also extended to include imidazolines (entries 1 and 2, Table 5), illustrating once again

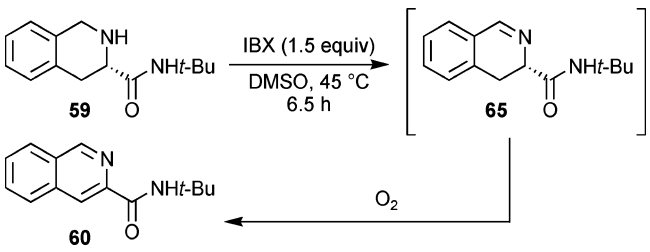
(29) (a) Lee, J.; U, J. S.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 10241. (b) Itoh, T.; Kaneda, K.; Teranishi, S. *Tetrahedron Lett.* **1975**, 2801.
(30) See, inter alia: (a) Mabic, S.; Castagnoli, N. *J. Med. Chem.* **1996**, *39*, 3694. (b) Macdonald, T. L.; Zirvi, K.; Burka, L. T.; Peyman, P.; Guengerich, F. P. *J. Am. Chem. Soc.* **1982**, *104*, 2050.
(31) Chow, Y. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. *Chem. Rev.* **1978**, *78*, 243.
(32) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2003.

Table 5. IBX-Mediated Synthesis of Substituted Imidazoles, Isoquinolines, Pyridines, and Pyrroles Starting from Cyclic Amines[a]

Entry	Substrate	Product	*t* (h)	Yield (%)[b]
1	 **54**	 **55**	14	71
2	 **56**	 **57**	16	81
3	 **26**	 **58**	23	82[c]
4	 **59**	 **60**	6.5	95
5	 **61**	 **62**	48	90
6	 **63**	 **64**	13	23[d]

[a] Reactions were conducted on 0.2−0.5 mmol scale in DMSO at 45 °C with 1.5 equiv IBX, unless otherwise noted. [b] Isolated yield with no chromatography necessary. [c] 2.5 equiv of IBX was employed. [d] Substrate polymerization was observed.

Scheme 5. Aromatization of Tetrahydroisoquinoline Substrate **59** through Initial IBX-Mediated Oxidation Followed by (Presumed) Autoxidation to Afford Isoquinoline **60**



the ability of IBX to mediate the oxidation of nitrogen functionalities in a variety of nonbenzylic systems, the susceptibility of *N*-methyl groups having already been presented (vide supra). The dehydrogenation of imidazolines, compounds readily available from alkyl cyanides and substituted diamines,[33,34] provides an efficient and direct route to a range of highly substituted imidazoles. A noteworthy example of this useful conversion is entry 2 (Table 5), in which **56** underwent straightforward conversion to the imidazole with the sensitive sulfide functionality left intact. The employment of conventional methods, utilizing palladium catalysis in refluxing toluene, would have been futile if applied to this substrate.[33,34]

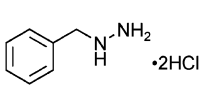
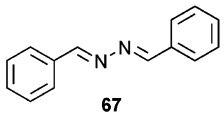
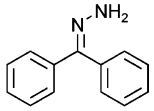
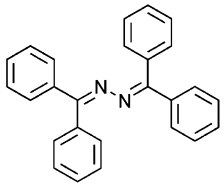
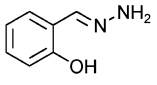
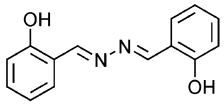
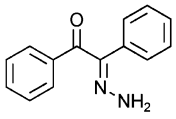
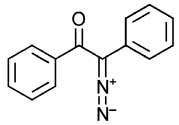
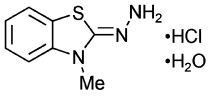
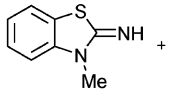
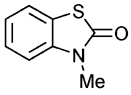
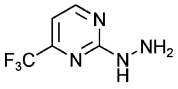
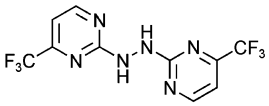
3. IBX-Mediated Oxidation of Hydrazines and Hydrazones. In the process of assessing a diverse range of nitrogen-containing substrates with IBX, hydrazines and hydrazones attracted our attention as it was envisioned that the oxidation of such compounds could perhaps offer a mode for the construction of substituted diazo species. Our interest in such a process was fueled by recent evidence suggesting that the biological activity of the kinamycin and lomaiviticin classes of natural products, resulting in DNA cleavage, is linked to the presence and characteristics of a diazo moiety.[35] A method involving the IBX-mediated oxidation of hydrazines could potentially provide a straightforward path to the synthesis of a range of diazo compounds for biological evaluation purposes. To test this hypothesis, the simple hydrazine derivative **66** was treated with IBX (entry 1, Table 6). However, when **66** was subjected to the standard protocol, an azine (**67**), rather than a diazo compound, was isolated. This result was not particularly surprising considering the relative instability of phenyldiazomethane, although the mechanism for the near quantitative formation of **67** now became the foremost question requiring an answer.

Upon exposure of compounds represented by the general structure **79** to IBX, hydrazone formation was presumably followed by further dehydrogenation to the corresponding diazo compound as shown in Scheme 6. The role of an intermediary diazo species in oxidations of this type (**79**, **80** → **82**) is reinforced by the violet color observed upon addition of IBX to benzophenone hydrazone (entry 2, Table 6), as this color is reportedly indicative of the presence of diphenyldiazomethane.[36] At this point, the postulated engagement of a second molecule of **81**, conceivably orchestrated by a Lewis acidic iodine center, initiates a net dimerization event to auspiciously afford the observed azine product **82**, whose generation is accompanied by the release of molecular nitrogen.

Analogous dimerizations have been reported in the literature. They can occur simply upon standing for certain susceptible hydrazones,[37] or by the use of rhodium(II) acetate catalysis[38] or stoichiometric bis(acetylacetonato)copper(II),[39] manganese dioxide,[36] mercuric oxide,[40] lead tetraacetate,[41] or iodine,[42] among other reagents.[43] Azine formation may also occur via irradiation of a diazo compound in the presence of a photosensitizer through a single electron-mediated oxidation; however, in these examples, the yields are low and a mixture of additional products was always observed.[44] From these precedents, it appears that such efficient construction of azines using IBX, as illustrated in Table 6 (entries 1−3), is suggestive of a key coordination and organizational role being played by the iodine center in the coupling step, in a mechanism redolent of certain transition-metal-mediated processes.[38,39] Entry 3, Table 6 is a

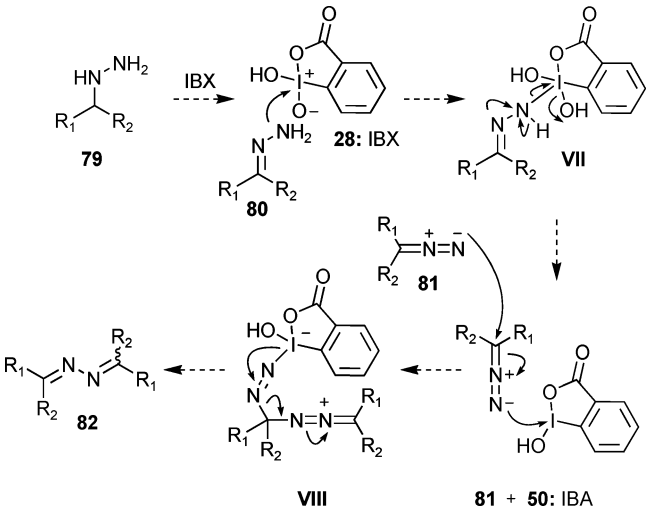
(33) Anastassiadou, M.; Baziard-Mouysset, G.; Payard, M. *Synthesis* **2000**, 1814.
(34) Amemiya, Y.; Miller, D. D.; Hsu, F.-L. *Synth. Commun.* **1990**, *20*, 2483.
(35) Laufer, R. S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **2002**, *124*, 1854.
(36) Barakat, M. Z.; Abdel-Wahab, M. F.; El-Sadr, M. M. *J. Chem. Soc.* **1956**, 4685.
(37) Kolb, V. M.; Kuffel, A. C.; Spiwek, H. O.; Janota, T. E. *J. Org. Chem.* **1989**, *54*, 2771.
(38) Shankar, B. K. R.; Shechter, H. *Tetrahedron Lett.* **1982**, *23*, 2277.
(39) (a) Ibata, T.; Singh, G. S. *Tetrahedron Lett.* **1994**, *35*, 2581. (b) Singh, G. S.; Singh, S. B.; Mehrotra, K. N. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1667.
(40) (a) Mustafa, A. *J. Chem. Soc.* **1949**, 352. (b) Day, A. C.; Raymond, P.; Southam, R. M.; Whiting, M. C. *J. Chem. Soc. C* **1966**, 467.
(41) Stojiljkovic, A.; Orbovic, N.; Sredojevic, S.; Mihailovic, M. L. *Tetrahedron* **1970**, *26*, 1101.
(42) Barton, D. M.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470.
(43) For a leading reference, see: Regitz, M. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; John Wiley & Sons: Chichester, U.K., 1978; Part 2, pp 659−708.
(44) Ishiguro, K.; Ikeda, M.; Sawaki, Y. *J. Org. Chem.* **1992**, *57*, 3057.

Table 6. IBX-Mediated Oxidation of Hydrazines and Hydrazones To Afford Azo-Dimers, Imines (Thioureas), and Diazo Compounds[a]

Entry	Substrate	Product(s)	Conditions	Yield (%)[b]
1	 **66**	 **67**	2.5 equiv IBX, 25 °C, 20 min	95
2	 **68**	 **69**	2.0 equiv IBX, 10 min, 25 °C; then 15 min, 45 °C	99
3	 **70**	 **71**	1.0 equiv IBX, 25 °C, 20 min	84
4	 **72**	 **73**	1.5 equiv IBX, 25 °C, 4 h	99
5	 **74**	 **75** +  **76**	1.5 equiv IBX, 25 °C, 20 min	99[c]
6	 **77**	 **78**	2.0 equiv IBX, 25 °C, 20 min	94

[a] Reactions were conducted on 0.2−0.5 mmol scale in DMSO. [b] Isolated yield with no chromatography necessary. [c] Product ratio of **75**:**76** observed to be 1.0:0.2 by ^{1}H NMR spectroscopy.

Scheme 6. Proposed Mechanism for the Oxidation of Hydrazones To Afford Diazo and Azine Products



notable example of this oxidative coupling as it demonstrates the preference for azine formation rather than the known rapid oxidation of the phenol to afford the corresponding *o*-quinone.[45]

This methodology should prove useful as azines have received attention resulting from their utility in unusual crisscross 1,3-dipolar cycloaddition reactions,[46] carbon−carbon bond-forming processes,[47] polymer synthesis,[48] and recently as ligands in the synthesis of novel organometallic compounds.[49] Presently, there are also at least two examples of azine natural products in the literature (agaricone[50] and limnazine[51]).

Not all hydrazine/hydrazone substrates provided azine products by means of exposure to oxidative conditions. Upon the addition of IBX to benzil monohydrazone (**72**), a bright yellow color was observed with no evolution of gas to provide the α-diazoketone **73** (entry 4, Table 6). Interestingly, the same reactivity trend was reported with bis(acetylacetonato)copper-(II), where the oxidation of benzil monohydrazone gave the diazo compound (**73**), and benzophenone hydrazone afforded the azine due to the formation of a copper carbene species.[39] Dimerization of **73** in the presence of IBX was likely precluded

(45) Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285.

(46) Bailey, J. R.; McPherson, A. T. *J. Am. Chem. Soc.* **1917**, *39*, 1322.
(47) Howard, L. B.; Hilbert, G. E.; Wiebe, R.; Gaddy, V. L. *J. Am. Chem. Soc.* **1932**, *54*, 3628.
(48) Kesslen, E. C.; Euler, W. B. *Chem. Mater.* **1999**, *11*, 336.
(49) Son, S. U.; Park, K. H.; Jung, I. G.; Chung, Y. K. *Organometallics* **2002**, *21*, 5366.
(50) Hilbig, S.; Andries, T.; Steglich, W.; Anke, T. *Angew. Chem.* **1985**, *97*, 1063.
(51) Asolkar, R. N.; Kamat, V. P.; Wagner-Dobler, I.; Laatsch, H. *J. Nat. Prod.* **2002**, *65*, 1664.

due to stabilization provided by the adjacent carbonyl, which hindered the addition of a second molecule of **73** upon iodine coordination. On the other hand, when IBX was added to a solution of the electron-rich hydrazone **74**, evolution of nitrogen preceded the formation of not an azine, but imine **75** (confirmed by X-ray analysis). It is postulated that **74** undergoes transformation to the imine via formation of a tetrazine intermediate (formed upon coupling of hydrazone **74** with the terminal nitrogen of a molecule of so-formed diazo compound), which can then decompose with the evolution of molecular nitrogen, perhaps in a manner similar to that reported in the treatment of **74** with lead tetraacetate.[52]

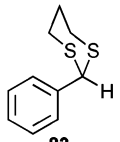
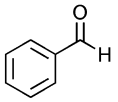
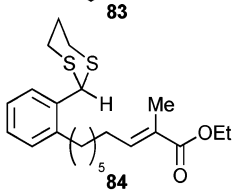
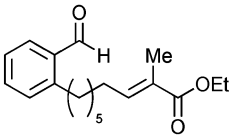
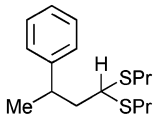
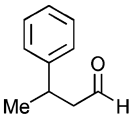
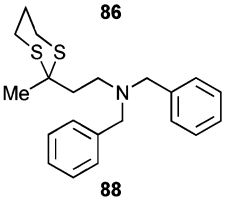
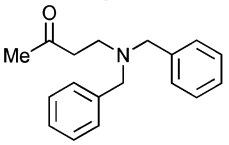
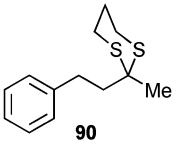
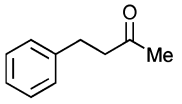
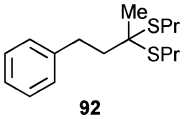
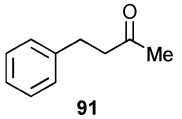
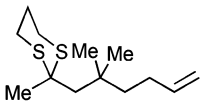
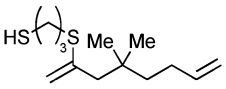
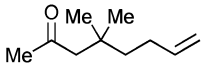
Finally, entry 6 represents the application of this method to the oxidative dimerization of an arylhydrazine. Interestingly, in this specific case, a final oxidation to the azo-compound was not observed, perhaps by virtue of steric factors or delocalization of the hydrazine lone pairs into the pyrimidine ring systems of **78**.

4. Oxidative Cleavage of Dithioacetals and Dithioketals (Dithianes) with IBX. Of the numerous methods known for the protection of carbonyl compounds, the application of dithioacetals and dithioketals is remarkably prevalent. The frequency of their occurrence is largely due to the ease of preparation and to their stability under both acidic and basic conditions.[53] Methods for their removal, however, are generally less straightforward and, until recently, often necessitated the use of harsh oxidative processes or mercury(II) salts.[54] A less toxic, general procedure for the cleavage of dithioacetals continued to elude chemists until the disclosure of the Stork−Zhao method in 1989, which utilized the reagent bis(trifluoroacetoxy)iodobenzene.[55] Although this method has proven valuable on a wide assortment of functionalized systems, the requisite liberation of trifluoroacetic acid in situ could be problematic when applied to sensitive substrates. Hence, an IBX-based methodology seemed to be an attractive alternative, as dithiane deprotection could be conducted under milder conditions. The affinity of various iodine reagents for sulfur has also been exploited in similar dethioacetalization procedures that have been recently communicated.[56−58]

In the process of ascertaining the viability of an IBX-mediated hydrolysis of dithianes, it was gratifying to find that 2-phenyl-1,3-dithiane (**83**), on treatment with IBX in wet DMSO, was successfully deprotected to furnish benzaldehyde in near quantitative yield (entry 1, Table 7). Encouraged by this result, additional derivatized dithioacetals and dithioketals (both cyclic and acyclic) were subjected to the protocol and smoothly afforded their carbonyl counterparts in admirable yield (Table 7). Notably, the inclusion of a tertiary benzylamine (entry 4, Table 7) proved not to impede dithiane hydrolysis, despite benzylic amines being recognized as retardants of other IBX-mediated reactions such as the oxidation of alcohols to their corresponding carbonyl compounds (vide infra). The addition of CH_2Cl_2 was often necessary to achieve complete solubility of the more lipophilic substrates, although its capability to encumber IBX chemistry has been verified in other contexts.[12,13] As Table 7 suggests, cleavage may proceed more rapidly in the case of unhindered benzylic dithioacetals (entry 1, Table 7); however, the IBX-mediated rupture of unactivated dithioketals is also a quite feasible undertaking (entries 3−8, Table 7), contrary to the implications of previously reported work.[56]

Interestingly, when compound **93** was engaged by IBX (entry 7, Table 7), vinyl sulfide **94**, not ketone **95**, was obtained, revealing that the adjacent *gem*-dimethyl group likely impedes the hydrolysis of the observed product. To test this hypothesis, substrate **93** was again treated with IBX, although this time in

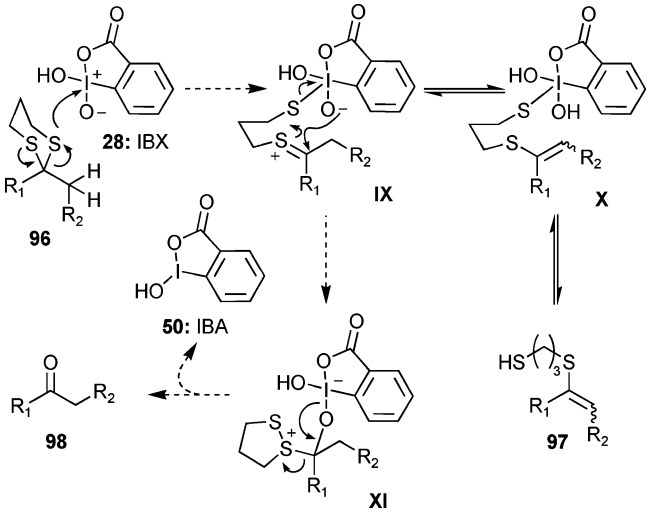
Table 7. IBX-Induced Cleavage of Dithioacetals and Dithioketals to Their Corresponding Carbonyl Compounds[a]

Entry	Substrate	Product	*t* (h)	Yield (%)[b]
1	 **83**	 **30**	0.3	99
2	 **84**	 **85**	24	99[c,d]
3	 **86**	 **87**	7	96[c]
4	 **88**	 **89**	6	96[e]
5	 **90**	 **91**	2	84[c]
6	 **92**	 **91**	1.5	99[c]
7	 **93**	 **94**	0.1	98[c]
8		 **95**	6	96[e]

[a] Reactions were conducted on 0.1−1.0 mmol scale in DMSO/H_2O (9:1) with 2.0 equiv of IBX at 25 °C. [b] Isolated yield with no purification required unless otherwise noted. [c] CH_2Cl_2 added to improve substrate solubility. [d] Based on recovered starting material (68% product, 31% recovered **84**). [e] 1−10 mol % AcOH added.

(52) Hunig, S.; Quast, H. *Justus Liebigs Ann. Chem.* **1968**, 139.
(53) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147.
(54) *Protective Groups in Organic Synthesis*, 3rd ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley & Sons: New York, 1999.
(55) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.
(56) Wu, Y.; Shen, X.; Huang, J.-H.; Tang, C.-J.; Liu, H.-H.; Hu, Q. *Tetrahedron Lett.* **2002**, *43*, 6443.
(57) Choudary, B. M.; Sudha, Y. *Synth. Commun.* **1996**, *26*, 2993.
(58) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 575.

Scheme 7. Postulated Mechanistic Rationale for the Deprotection of Dithianes by IBX under Neutral Conditions

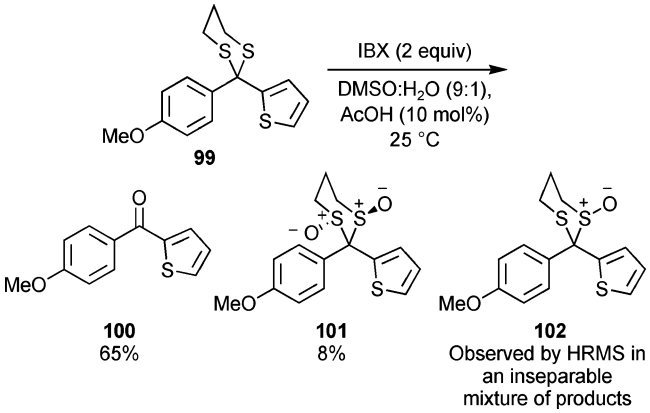


the presence of acetic acid, added to assist in the hydrolysis step. On this occasion, as expected, carbonyl **95** was isolated in superb yield with the terminal olefin left intact. From these insightful results, a reasonable mechanism for the deprotection of dithianes induced by IBX was subsequently proposed and is presented in Scheme 7. Upon association of the protected compounds of type **96** with IBX, assistance from the neighboring dithiane sulfur atom presumably leads to the fragmented sulfonium intermediate **IX**. When no hydrogens are present adjacent to the sulfonium cation, as must be the case in entry 1, Table 7, the oxide ligand of IBX (or H_2O) next attacks the sulfonium intermediate **IX** to afford the mixed thioacetal, which then finally rearranges to furnish the carbonyl product. The same pathway could also be followed when there are hydrogen substituents adjacent to the sulfonium intermediate **IX**; however, isolation of vinyl sulfide **94** would suggest another feasible option whereupon the basic oxide ligand of the iodine species could facilitate the abstraction of an α-proton intramolecularly to generate intermediates of type **X** (this process is essentially a tautomerization). From this point, the substrate may dissociate from IBX to reveal a compound of type **97**. Although the cyclic disulfide, as depicted in Scheme 7, was never directly observed in the course of our research, the presence of the analogous compound, dipropyl disulfide, was substantiated (^{1}H NMR and GC/MS) in experiments whose results are summarized in entries 3 and 6, Table 7.

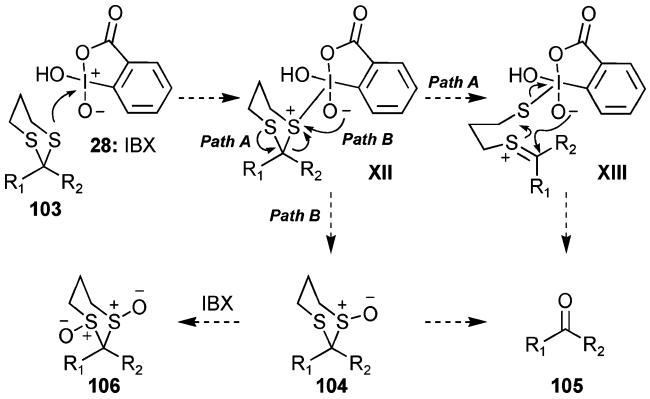
Although cleavage proceeded efficiently in the range of examples shown in Table 7, the analysis of a more sterically encumbered dithiane (containing no α-hydrogens) revealed that oxidative cleavage via IBX is less easily accomplished (Scheme 8). Thus, compound **99**, on treatment with IBX, yielded not only the ketone **100**, as expected, but also a range of sulfoxide products, including the asymmetric disulfoxide **101**[59] and monosulfoxide **102** (observed by HRMS). This example indicates that when hydrolysis is impeded due to sterics, and a route to the vinyl sulfide is lacking (vide supra), sulfoxide formation can become a more favorable process. A mechanistic rationale for these observations is presented in Scheme 9.

5. IBX Relative Reactivity. In the process of fully assessing the range and compatibility of IBX-mediated transformations,

Scheme 8. IBX-Mediated Deprotection of **99**: An Example of a Dithiane Lacking α-Hydrogens



Scheme 9. Postulated Mechanistic Rationale for the Deprotection of Sterically Hindered Dithianes, Lacking α-Hydrogens, by IBX



it became relevant to ascertain whether the aforementioned amine chemistry proceeds with preference over inherent reactivity in other functional groups known to be susceptible to IBX, such as an alcohol,[27] carbonyl,[5,11,12] and dithiane (vide supra). As such, a series of competition experiments were conducted, with their results displayed in Table 8. Remarkably, in the presence of a secondary alcohol (**107**), α,*β*-saturated ketone (**108**), and dithiane moiety (**109**), imine formation was, in each case, convincingly favored. However, in the specific case where ketone α,*β*-unsaturation was evaluated in the presence of dibenzylamine (entry 2, Table 8), *N*-benzylidene formation was not entirely complete, as substrate degradation regrettably became a factor with increased equivalents of IBX.

Conclusion

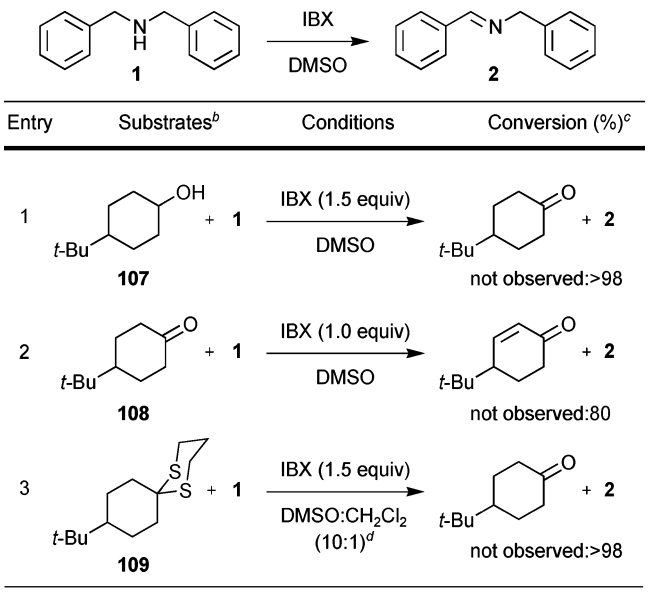
In conclusion, recent studies have verified that the applications of hypervalent iodine(V) research have swelled beyond the realm of simple alcohol oxidation, to include a wide array of synthetically relevant transformations, as has been previously accomplished with iodine(III) reagents. This surge has been initiated, at least in part, by the effective rediscovery of IBX within recent decades, in addition to an improved method for its preparation.[60] However, it is still widely accepted that considerable voids yet remain in this fledgling area of research.

In our attempt to broaden the scope and generality of IBX-mediated chemistry, we drew upon the understanding that IBX readily accepts new heteroatom-bearing ligands and, subsequently, were able to establish that IBX facilitates a range of

(59) For evidence of an analogous asymmetric disulfoxide, see: Bulman Page, P. C.; Wilkes, R. D.; Namwindwa, E. S.; Witty, M. J. *Tetrahedron* **1996**, *52*, 2125.

(60) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

Table 8. Relative Reactivity of IBX toward Secondary Amine **1** versus Alcohol **107**, Ketone **108**, and Dithiane **109**[a]



[a] Reactions were conducted on 0.2−0.5 mmol scale at 45 °C for 45 min. [b] 1.0 equiv each of **1** and **107**, **108**, or **109** was used. [c] Determined by ^{1}H NMR spectroscopy. [d] CH_2Cl_2 was used to improve substrate solubility.

reactions instituting both nitrogen- and sulfur-containing substrates. In particular, we have developed a considerably mild approach to the construction of imines from precursor secondary amines through the use of IBX. The utility of this methodology is highlighted by the admirable yields, in addition to a great degree of functional group tolerance reported. Interestingly, this chemistry also presents a paradigm for the facile deprotection of secondary *N*-benzylamines to their primary counterparts.

Furthermore, in this work we have described the facile oxidative aromatization of nitrogen heterocycles, notably including substrates that boast no activating group, along with novel transformations pertaining to the oxidation of hydrazine and hydrazone substrates. Finally, a general, yet tolerant, protocol for the cleavage of dithioacetals and dithioketals has been unveiled, with a relevant mechanistic proposal sufficiently espoused. These achievements, in total, have set a critical precedent in IBX-based research and portend the further expansion and development of relevant iodine(V)-mediated chemistry. Despite the novelty and potential use of this chemistry, however, we wish to underscore the caution by which we recommend the preparation and reactions of IBX be carried out. This cautionary note stems from a personal communication with Dr. Jeremiah P. Freeman who informed us that Merck scientists observed explosions with IBX under test conditions. Reactions should therefore be carried out behind protecting shields, and high temperatures should be avoided.

Experimental Section

CAUTION: *The preparation and use of IBX may be accompanied by explosions at high-temperature conditions!*

General Procedure for IBX-Induced Oxidation of Amines. Procedure A: IBX (92 mg, 0.33 mmol) was dissolved in DMSO (0.5 mL) with vigorous stirring for approximately 30 min. This IBX solution was then added to a solution of amine (0.30 mmol) in DMSO (0.5 mL) and stirred at room temperature for ca. 10−20 min, or until starting material had been consumed. The mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (1 mL) and then basified with saturated aqueous $NaHCO_3$ (1 mL). Following extraction with EtOAc (5 mL), the organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to yield the desired product. Generally, no purification was necessary. Procedure B: IBX (92 mg, 0.33 mmol) was added as a solid to a solution of amine (0.30 mmol) in DMSO (1 mL) and stirred at 45 °C for 0.3−14 h. The mixture was cooled to room temperature and quenched by addition of saturated aqueous $Na_2S_2O_3$ (1 mL) and then basified with saturated aqueous $NaHCO_3$ (1 mL). Following extraction with EtOAc (5 mL), the organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to yield the desired product. Generally, no purification is necessary.

General Procedure for the Oxidative Coupling of Hydrazines/Hydrazones. IBX (84−210 mg, 0.30−0.75 mmol) was carefully added as a solid to a solution of hydrazine/hydrazone (0.30 mmol) in DMSO (1.0 mL). The reaction mixture was stirred at room temperature for approximately 20 min until gas evolution had ceased. The mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (1 mL) and then basified with 1 M KOH or $NaHCO_3$ (1 mL). Following extraction with EtOAc (5 mL), the organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to yield the corresponding azine/hydrazine, which could be purified by flash column chromatography (silica gel), if necessary.

General Procedure for the Oxidative Armatization of *N*-Heterocycles. IBX (126 mg, 0.45 mmol) was added to a solution of imidazoline (0.30 mmol) in DMSO (1.0 mL). The reaction mixture was stirred at 45 °C until complete consumption of starting material was observed by thin-layer chromatography (TLC), and the mixture was then quenched by addition of saturated aqueous $Na_2S_2O_3$ (1 mL). The mixture was basified with 1 M KOH (1 mL) and extracted with EtOAc (5 mL). The organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to afford the corresponding imidazole, which could be purified by flash column chromatography (silica gel), if necessary.

General Procedure for the Deprotection of Dithianes. IBX (168 mg, 0.60 mmol) was dissolved in DMSO (0.5 mL) with vigorous stirring for approximately 30 min at ambient temperature. This IBX solution was then added to a solution of dithiane (0.30 mmol) in DMSO/H_2O (4:1, 0.5 mL) and stirred at room temperature. Addition of CH_2Cl_2 was only undertaken as needed to ensure substrate solubility. The reaction was monitored by TLC until complete consumption of starting material was observed. The mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (1 mL) and then basified with saturated aqueous $NaHCO_3$ (1 mL). Following extraction with ether (5 mL), the organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to yield the anticipated carbonyl compound, which could be purified by flash column chromatography (silica gel), if necessary.

Acknowledgment. We thank Drs. D. H. Huang, G. Siuzdak, and R. Chadha for NMR spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. This work was financially supported by the National Institutes of Health (U.S.A.), The Skaggs Institute for Chemical Biology, Merck, and Pfizer.

Supporting Information Available: Experimental procedures, compound characterization, and selected ^{1}H and ^{13}C NMR spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0400382