

Recent Advances in IBX-Mediated Oxidative Desulfurization for the Synthesis of Azoles

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Abstract:

This review presents a systematic overview of the thiophilic properties of *o*-iodoxybenzoic acid (IBX) and its application in oxidative desulfurization processes that promote domino transformations toward the synthesis of diverse azoles. Particular emphasis is placed on IBX-mediated oxidative strategies for the efficient construction of highly substituted oxadiazoles, thiadiazoles, triazoles, and tetrazoles. The review highlights the versatility of readily accessible sulfur-containing precursors, including thiosemicarbazides, bis(diaryl)thioureas, 1,3-disubstituted thioureas, and thioamides, as valuable starting materials for these transformations. The reported methodologies generally provide the desired azole derivatives in good to excellent yields, demonstrating the potential of IBX as an effective and versatile reagent for oxidative desulfurization and domino cyclization reactions. Overall, these developments underscore the significance of IBX-mediated sulfur-to-nitrogen/oxygen transformations as useful approaches for the sustainable synthesis of structurally diverse and biologically relevant azole frameworks.

Introduction

Azoles constitute an important class of nitrogen- and heteroatom-containing heterocycles that occupy a prominent position in medicinal chemistry and the pharmaceutical industry because of their diverse biological activities and structural versatility. Beyond pharmaceutical applications, azole-based compounds have found significant utility in agrochemical development, materials science, and other areas of chemical research. Consequently, the development of efficient, concise, and operationally simple synthetic strategies for the construction of azole frameworks continues to be an important area of contemporary organic chemistry.

Among the various reagents developed for modern organic synthesis, hypervalent iodine compounds have emerged as versatile and powerful reagents for a broad range of oxidative and bond-forming transformations. In particular, hypervalent iodine(V) reagents have attracted considerable attention because of their mild reaction conditions, high functional-group tolerance, and ability to facilitate carbon-carbon and carbon-heteroatom bond formation. These characteristics have contributed to their extensive application in medicinal chemistry, natural product synthesis, and the preparation of structurally complex organic molecules.

Oxidative desulfurization represents one of the useful reaction pathways enabled by hypervalent iodine chemistry. Although several hypervalent iodine reagents have been investigated for sulfur-mediated transformations, the specific chemistry of *o*-iodoxybenzoic acid (IBX) with sulfur-containing substrates remains comparatively less explored. Early studies demonstrated the utility of IBX in transformations such as the deprotection of dithianes, while subsequent investigations have expanded the scope of IBX-mediated sulfur chemistry considerably. These studies have established IBX as an effective reagent for a variety of sulfur-centered oxidative transformations, including the oxidation of sulfides to sulfoxides, oxidative ring-expansion reactions of sulfur-containing heterocycles, oxidative dimerization of thioamides to 1,2,4-thiadiazoles, and oxidative desulfurization of 1,3-disubstituted thioureas to the corresponding carbodiimides.

The progressive understanding of IBX-sulfur interactions has opened new opportunities for exploiting oxidative desulfurization as a strategic tool in heterocyclic synthesis. In particular, the formation of carbodiimides from thioureas provides a valuable synthetic platform because carbodiimides are highly reactive intermediates capable of undergoing subsequent cyclization and functional-group transformations. This reactivity offers an attractive pathway for the development of one-pot and domino processes leading to structurally diverse nitrogen-containing heterocycles.

Building upon these advances, IBX-mediated oxidative desulfurization has evolved as a promising approach for the construction of diverse azole frameworks from readily accessible sulfur-containing precursors. The combination of oxidative desulfurization and subsequent intramolecular or intermolecular cyclization enables the development of concise synthetic routes with considerable functional-group compatibility. This review therefore focuses on the development of IBX-mediated sulfur chemistry, with particular emphasis on oxidative desulfurization and its application in domino and one-pot strategies for the synthesis of oxadiazoles, thiadiazoles, triazoles, tetrazoles, and related azole scaffolds. The mechanistic aspects, substrate scope, synthetic advantages, and potential applications of these transformations are also discussed to highlight the broader significance of IBX in modern heterocyclic synthesis.

Results and Discussion

The distinctive reactivity of IBX toward sulfur-containing functional groups provides a useful platform for oxidative desulfurization followed by cyclization. Based on the established ability of IBX to convert thiourea derivatives into reactive carbodiimide intermediates, a general strategy was conceived in which the in situ generated carbodiimides could undergo intra- or intermolecular trapping by suitable nucleophiles. This concept enabled the development of concise domino and one-pot approaches for the synthesis of diverse azole frameworks. The major transformations developed from this strategy are discussed below.

Synthesis of 2-Amino-1,3,4-oxadiazoles

One of the important applications of this methodology is the synthesis of 2-amino-1,3,4-oxadiazoles from readily accessible thiosemicarbazide precursors. The proposed reaction pathway involves IBX-mediated oxidative desulfurization of thiosemicarbazide **2** to generate a carbodiimide intermediate (A), which subsequently undergoes favorable intramolecular oxidative cyclization to furnish the corresponding 2-amino-1,3,4-oxadiazole **3**. The intramolecular nature of the cyclization is particularly advantageous from an entropic perspective and contributes to the efficiency of the transformation.

The synthetic importance of 2-amino-1,3,4-oxadiazoles arises from their broad range of biological and technological applications. These heterocycles have been associated with anti-inflammatory, analgesic, antihypertensive, diuretic, anticonvulsant, muscle-relaxant, antineoplastic, insecticidal, and herbicidal activities. In addition to their significance in medicinal and agricultural chemistry, 1,3,4-oxadiazole derivatives have attracted attention in materials science, particularly as photosensitizers, liquid-crystalline materials, and electron-transporting components in organic light-emitting devices.

Despite their considerable synthetic and application-oriented importance, relatively mild and efficient methods for accessing 2-amino-1,3,4-oxadiazoles have been comparatively limited.

Scheme 1. IBX-Mediated Domino Reactions and Synthesis of Azoles

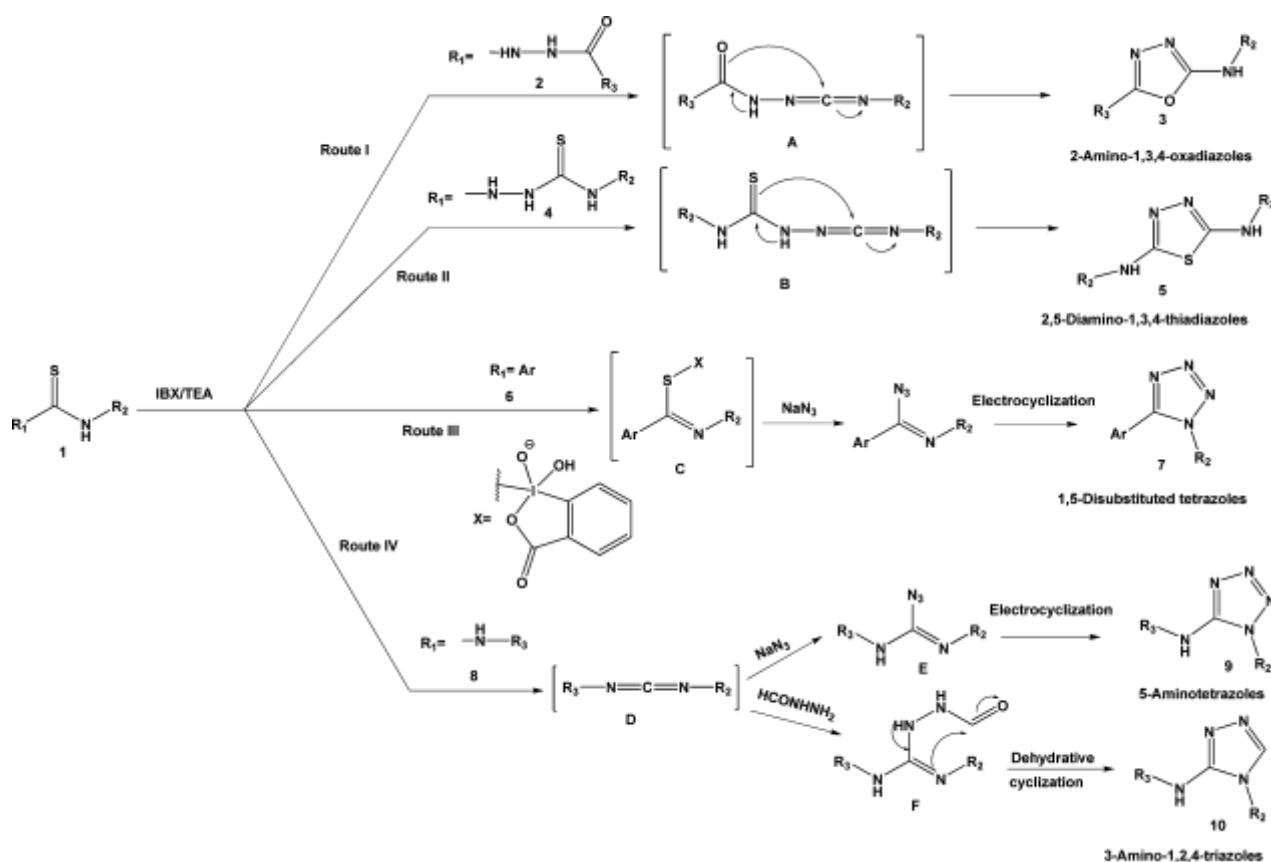
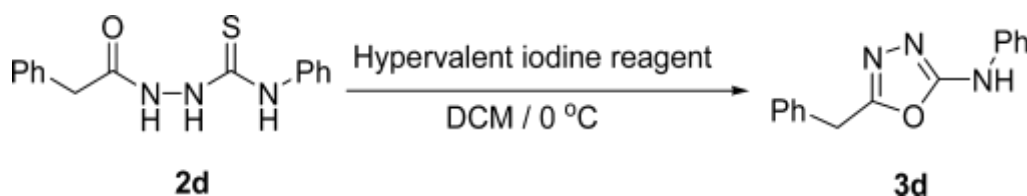


Table 1. Optimization of Reaction Conditions

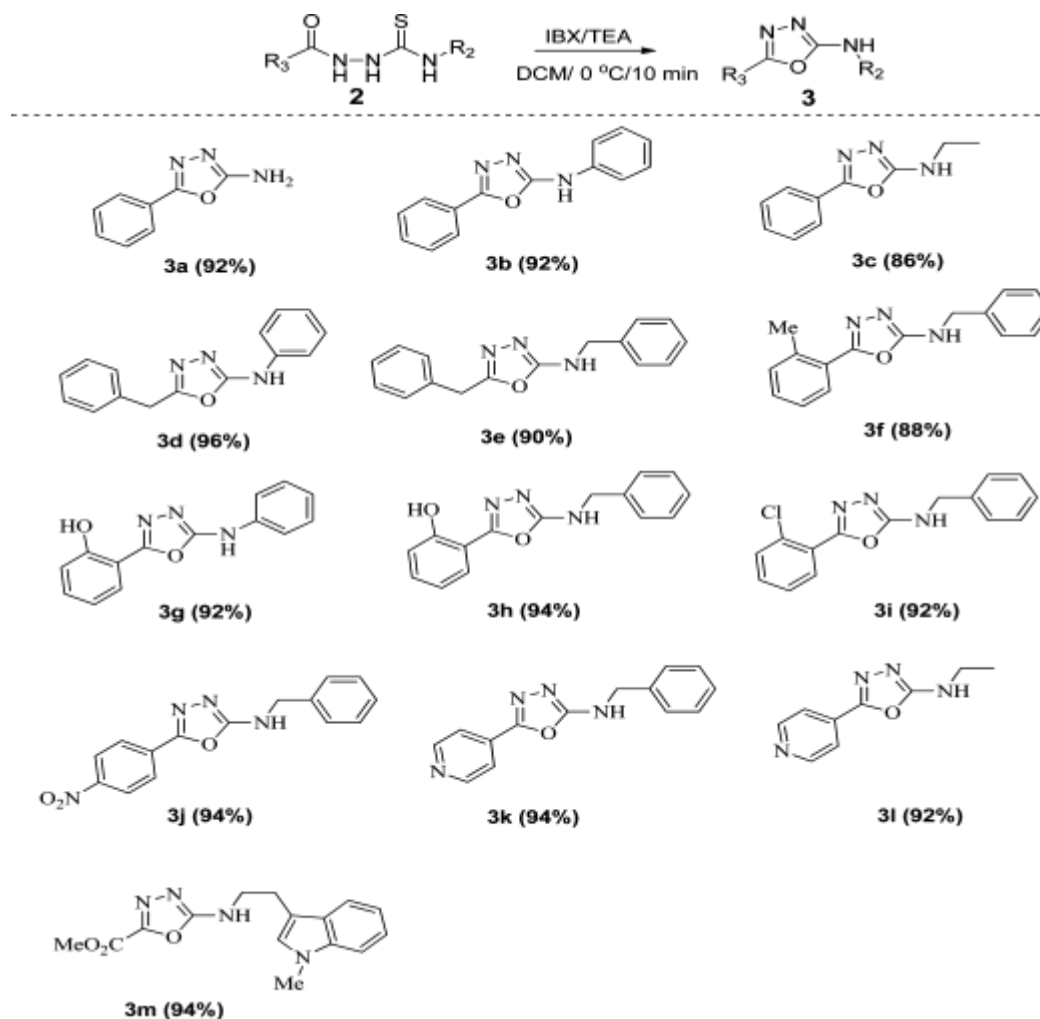


entry	hypervalent iodine reagent	TEA (equiv)	time (min)	yield ^b (%)
1	DIB	nil	360	78
2	IBX	nil	360	68
3	DMP	nil	360	65
4	DIB	2	10	84
5	IBX	2	10	96
6	DMP	2	10	80
7	IBX	1	60	70

Reported synthetic strategies can broadly be divided into two major approaches. The first involves cyclodehydration of semicarbazides using strong dehydrating systems such as phosphorus oxychloride, thionyl chloride, concentrated sulfuric acid, Burgess reagent, Appel-type reagents, and phosphonium reagents. The second approach relies on cyclodesulfurization of thiosemicarbazides employing reagents such as iodine/base systems, tosyl chloride, alkylating agents, carbodiimides, mercury salts, and lead oxide. Although effective, several of these procedures are associated with limitations including harsh reaction conditions, corrosive or toxic reagents, complicated reaction mixtures, and the formation of undesirable by-products.

In this context, the IBX/triethylamine (TEA) system represents a significant improvement, providing a comparatively mild and efficient oxidative cyclization protocol. Optimization studies were initially performed using 4-phenyl-1-(2-phenylacetyl)thiosemicarbazide (**2d**) as a model substrate. The reaction parameters, including the nature of the hypervalent iodine reagent, amount of TEA, reaction time, and solvent, were systematically evaluated. Among the hypervalent iodine reagents examined, IBX afforded the desired product **3d** in superior yield compared with Dess–Martin periodinane (DMP) and diacetoxyiodobenzene (DIB), either alone or in combination with TEA. The efficiency of the transformation was also strongly dependent on the amount of base, with a significant decrease in product formation observed when the quantity of TEA was reduced.

Table 2. Substrate Scope for 2-Amino-1,3,4-oxadiazoles



Several solvents, including DMSO, acetonitrile, ethyl acetate, and THF, were found to support the transformation. However, dichloromethane provided the cleanest reaction profile and was therefore identified as the preferred reaction medium. Collectively, the optimization studies established the IBX/TEA system as an effective combination for the oxidative cyclization of thiosemicarbazides to 2-amino-1,3,4-oxadiazoles.

The substrate scope of the transformation was subsequently investigated using a variety of substituted thiosemicarbazides. A broad range of 2-amino-1,3,4-oxadiazoles **3** was obtained in good to excellent yields, demonstrating the generality and functional-group tolerance of the method. Remarkably, most reactions proceeded rapidly and were completed within approximately 10 min. The reaction efficiency was largely unaffected by the electronic nature of substituents present on the aromatic rings, with both electron-rich and electron-deficient substrates undergoing efficient conversion.

An important feature of the methodology is its high chemoselectivity. Although IBX is known to oxidize phenolic substrates to the corresponding quinones, particularly under mild conditions, no detectable phenol oxidation products

were observed for the phenolic substrates examined. This observation highlights the selectivity of the IBX/TEA system toward the sulfur-containing functionality under the reaction conditions.

The synthetic utility of the methodology was further demonstrated through the preparation of methyl 5-[2-(1-methyl-1H-indol-3-yl)ethylamino]-1,3,4-oxadiazole-2-carboxylate. This compound is of particular interest because it has been employed as a common heterodiene intermediate in the synthesis of vinca alkaloids. Thus, the IBX-mediated oxidative cyclization strategy not only provides rapid access to structurally diverse 2-amino-1,3,4-oxadiazoles but also demonstrates potential utility for the preparation of synthetically valuable heterocyclic building blocks.

Overall, this transformation illustrates the broader potential of IBX-mediated oxidative desulfurization as a strategic approach to heterocycle synthesis. The combination of mild reaction conditions, short reaction times, good to excellent yields, broad substrate tolerance, and high chemoselectivity makes the IBX/TEA protocol an attractive alternative to conventional cyclodesulfurization and cyclodehydration procedures.

Mechanistic Aspects and Extension of IBX-Mediated Azole Synthesis

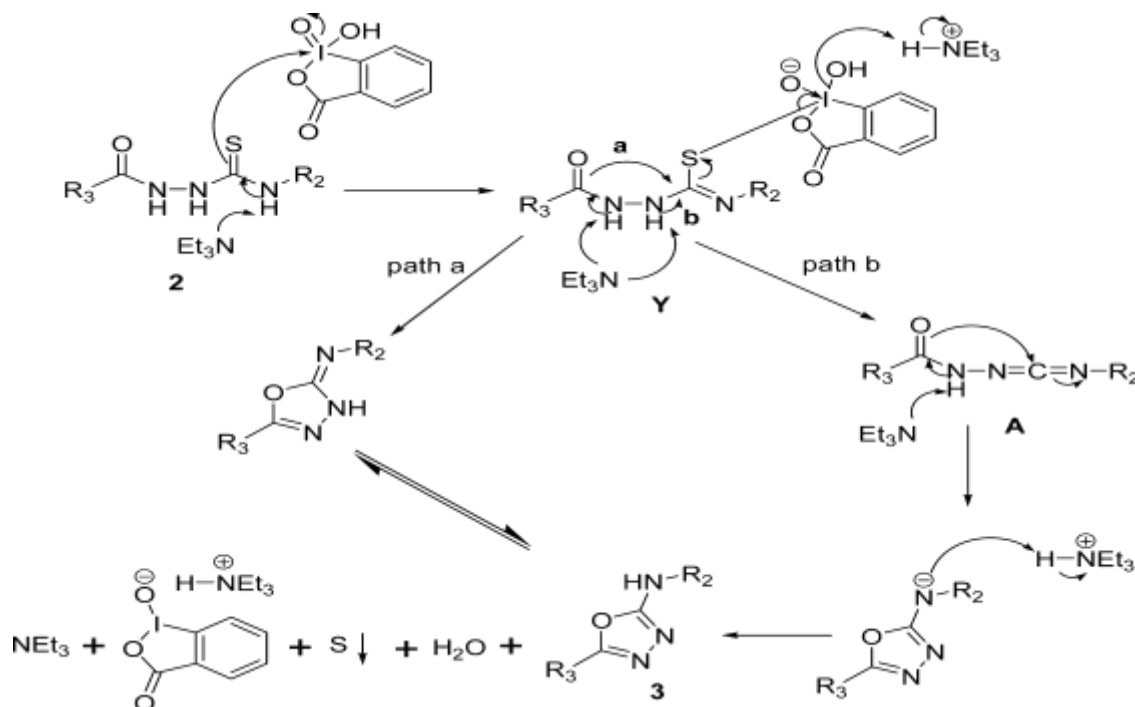
Proposed Mechanism for the Formation of 2-Amino-1,3,4-oxadiazoles

Based on the available literature concerning hypervalent iodine-mediated oxidative desulfurization, a plausible mechanistic pathway has been proposed for the IBX/triethylamine (TEA)-mediated synthesis of 2-amino-1,3,4-oxadiazoles. The proposed mechanism involves initial activation of the sulfur-containing substrate through interaction with the electrophilic iodine center of IBX. Nucleophilic attack of the sulfur atom at the iodine center, assisted by TEA, is proposed to generate an activated intermediate (Y). This intermediate may subsequently undergo transformation through two closely related pathways.

In the first pathway (path a), displacement of the sulfur functionality by oxygen followed by intramolecular cyclization generates the oxadiazole framework, which subsequently undergoes tautomerization to furnish the thermodynamically favored 2-amino-1,3,4-oxadiazole. Alternatively, in path b, oxidative desulfurization proceeds through formation of a carbodiimide intermediate (A), which subsequently undergoes intramolecular cyclization to produce the same heterocyclic product. The observation of elemental sulfur during the reaction provides experimental support for the occurrence of an oxidative desulfurization process.

Triethylamine appears to play a multifunctional role in this transformation. In addition to acting as a base, TEA facilitates the solubilization or activation of IBX in the reaction medium and promotes the reactivity of hydrazide/thiosemicarbazide functionalities. Its participation in substrate activation and in the subsequent cyclization steps may therefore contribute significantly to the efficiency of the overall transformation.

Scheme 2. Representative Postulated Mechanism of Desulfurization for Synthesis of 2-Amino-1,3,4-oxadiazoles and Role of TEA



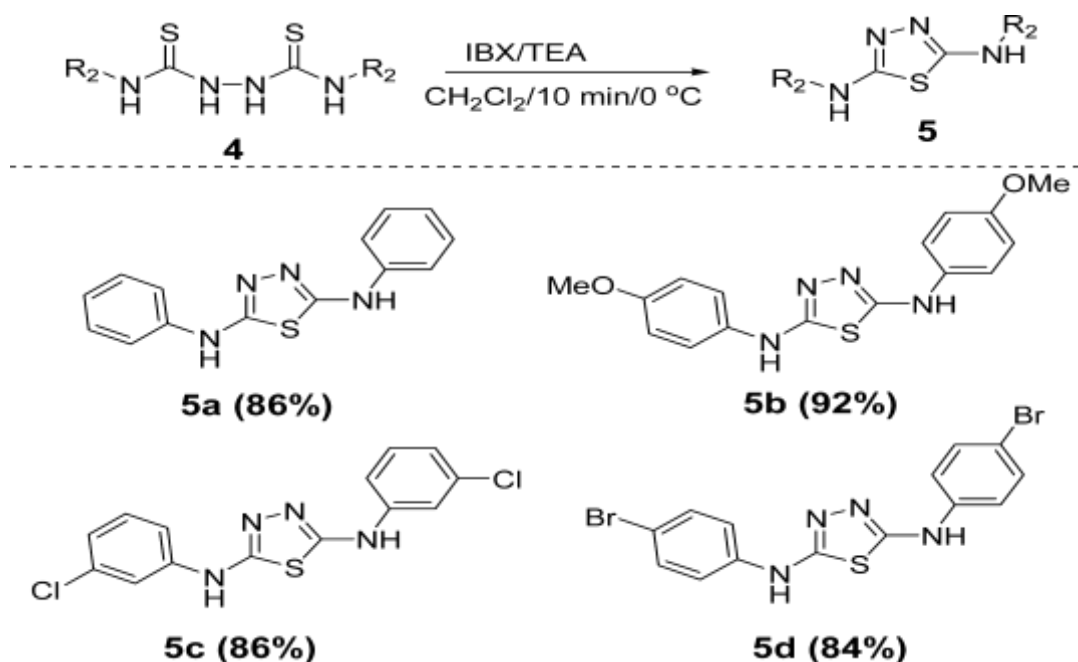
Synthesis of 2,5-Diamino-1,3,4-thiadiazoles

The successful application of IBX-mediated oxidative desulfurization to thiosemicarbazides prompted further exploration of its utility for the synthesis of other biologically relevant azoles. Among these, 1,3,4-thiadiazoles represent an important class of heterocyclic compounds because of their broad spectrum of biological activities. The increasing prevalence of resistance to conventional antimicrobial agents has intensified the search for new molecular scaffolds with antibacterial, antifungal, antiviral, and antitubercular properties. In this context, 1,3,4-thiadiazole derivatives have received considerable attention in medicinal chemistry owing to their reported antimicrobial, antituberculosis, anti-inflammatory, anticonvulsant, antioxidant, and antifungal activities.

Although numerous synthetic approaches to 1,3,4-thiadiazoles have been developed using diverse starting materials, oxidative cyclization of bis-diarylthioureas remains comparatively less explored. A major limitation of several reported procedures is the formation of multiple by-products, which complicates product isolation and purification. Conventional alkali-mediated thermal cyclization of bis-diarylthioureas generally provides 2,5-diamino-1,3,4-thiadiazoles in poor yields. Attempts to improve the transformation through microwave irradiation have not provided significant advantages and may result in complex reaction mixtures that are difficult to separate.

Several desulfurizing reagents, including chloranil, bromonil, and iodine, have subsequently been investigated for this conversion. Among these approaches, iodine-mediated procedures have demonstrated comparatively better yields; nevertheless, the development of alternative, efficient, and operationally simple oxidative systems remains desirable.

Table 3. Representative Examples for 2,5-Diamino-1,3,4-thiadiazoles



In this context, the IBX/TEA system provides an effective strategy for the oxidative cyclization of bis-diaryltioureas to 2,5-diamino-1,3,4-thiadiazoles. The transformation can be performed under conditions similar to those established for the synthesis of 2-amino-1,3,4-oxadiazoles, highlighting the versatility of the IBX-mediated oxidative desulfurization platform. The substrate-scope studies demonstrated that the electronic nature of the substituent significantly influences the reaction efficiency. Bis-diaryltioureas bearing electron-donating substituents generally afforded the corresponding thiadiazoles in higher yields, whereas substrates containing electron-withdrawing substituents exhibited comparatively lower conversions. These observations indicate that electronic effects play an important role in the oxidative cyclization process.

IBX-Mediated Synthesis of 1,5-Disubstituted Tetrazoles

The versatility of IBX-mediated oxidative desulfurization was further demonstrated through the synthesis of 1,5-disubstituted tetrazoles from thioamides. On the basis of the established reactivity of IBX toward sulfur-containing functionalities, it was proposed that oxidative activation of thioamide **6** could generate an electrophilic intermediate (**C**), which may undergo nucleophilic displacement by azide ion followed by electrocyclization to furnish the corresponding 1,5-disubstituted tetrazole **7**.

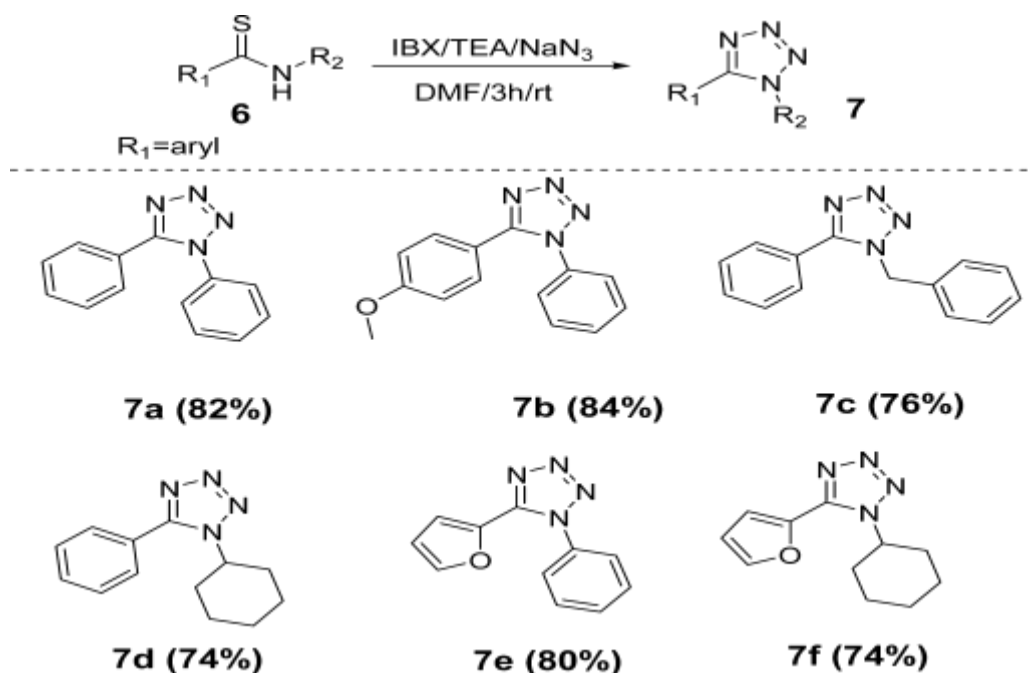
Tetrazoles occupy an important position in medicinal chemistry because they can function as bioisosteric replacements for cis-amide and carboxylic acid functionalities while offering opportunities for modulation of physicochemical properties such as lipophilicity. Consequently, tetrazole-containing compounds have been investigated in several therapeutic areas, including NAD(P)H oxidase inhibition, glucokinase activation, hepatitis C virus protease inhibition, and calcitonin gene-related peptide receptor antagonism. Tetrazoles also serve as valuable synthetic intermediates in the preparation of biologically active molecules.

A variety of methodologies have been developed for the synthesis of 1,5-disubstituted tetrazoles. Recent approaches include metal-catalyzed cross-coupling reactions, such as Suzuki–Miyaura and Negishi transformations, as well as direct C–H arylation and alkenylation of substituted tetrazoles. Alternative strategies employ secondary amides or thioamides in combination with reagents such as phosphorus pentachloride/hydrazoic acid, trimethylsilyl azide–triphenylphosphine/DEAD, and trimethylsilyl azide/triethylamine/mercuric(II) systems. Despite their utility, several of

these procedures are associated with disadvantages including prolonged reaction times, laborious work-up procedures, and the use of toxic or environmentally undesirable metal reagents.

The IBX/TEA protocol provides an alternative oxidative approach to 1,5-disubstituted tetrazoles and was investigated using a range of aryl- and heteroaryl-containing thioamides. The reaction exhibited good substrate tolerance, although the nature of the substituents influenced the isolated yields. 1,5-Diaryl tetrazoles were generally obtained in high yields, whereas substrates containing an alkyl group at one of the substitution sites afforded comparatively lower yields. An additional noteworthy feature of this methodology was the compatibility of acid-sensitive heteroaromatic functionalities. In particular, furan-containing substrates underwent successful conversion without detectable degradation of the furan ring, demonstrating the chemoselectivity and functional-group tolerance of the reaction conditions.

Table 4. Substrate Scope for 1,5-Disubstituted Tetrazoles



Collectively, these studies demonstrate that the IBX/TEA system can serve as a versatile oxidative platform for the construction of structurally diverse azoles. Its applicability to oxadiazoles, thiadiazoles, and tetrazoles illustrates the broader potential of hypervalent iodine-mediated oxidative desulfurization for developing concise and efficient heterocyclic synthesis.

Synthesis of 5-Aminotetrazoles

The successful application of IBX-mediated oxidative desulfurization to the synthesis of 1,5-disubstituted tetrazoles prompted further investigation into the reactivity of the carbodiimide intermediates generated from thioureas. It was envisaged that, rather than undergoing intramolecular transformations, these reactive carbodiimide intermediates could be intercepted by external nucleophiles. In particular, nucleophilic trapping with sodium azide was anticipated to provide an efficient route to 5-aminotetrazoles, whereas reaction with hydrazides could potentially furnish 1,2,4-triazoles. This concept provided a useful extension of the IBX-mediated oxidative desulfurization strategy toward the synthesis of additional nitrogen-rich heterocycles.

5-Aminotetrazoles represent an important class of nitrogen-rich compounds with applications extending across medicinal chemistry, materials science, and synthetic chemistry. Their high nitrogen content makes them attractive candidates for high-energy-density materials, while their ability to coordinate metal centers has led to their use as

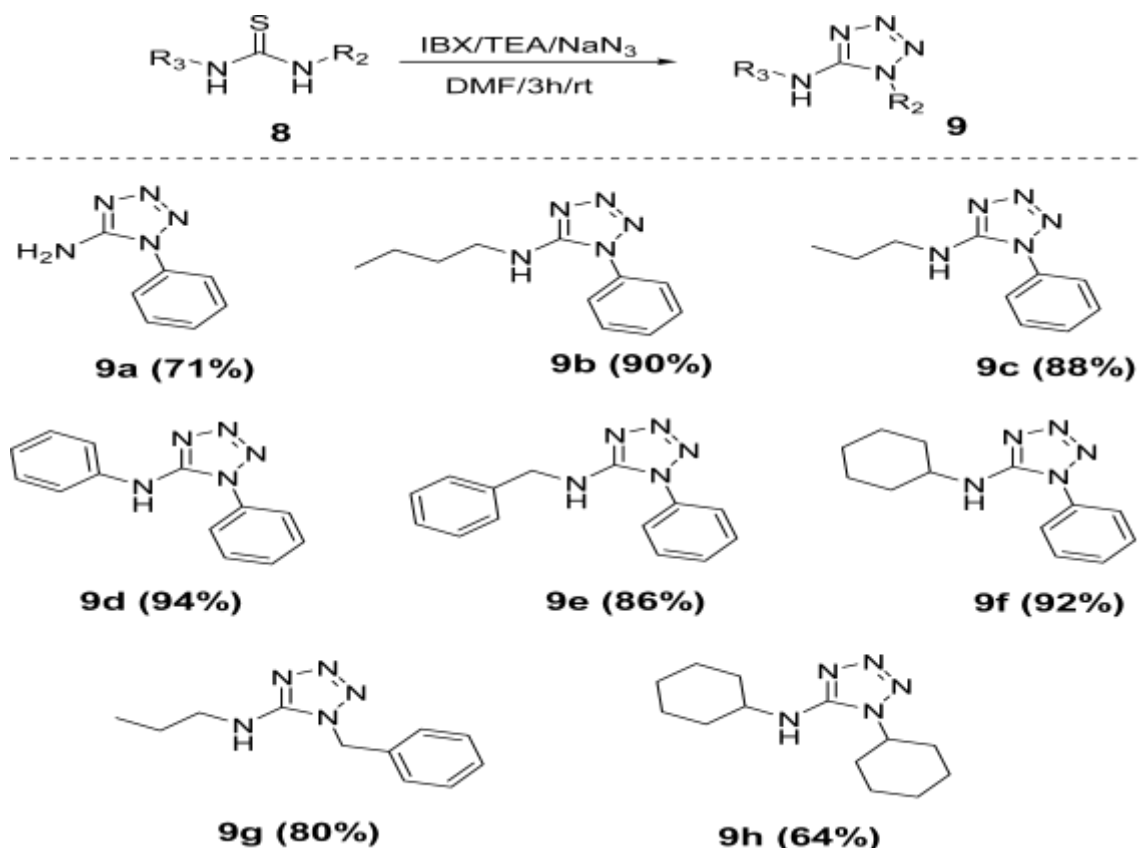
ligands. Furthermore, 5-aminotetrazoles serve as valuable synthetic intermediates in the preparation of biologically active pharmaceutical and natural-product-derived molecules.

Several approaches have been reported for the preparation of 5-(substituted amino)tetrazoles. These methodologies can broadly be classified into four categories: functionalization of the amino group or tetrazole ring of preformed 5-aminotetrazoles; nucleophilic displacement of suitable leaving groups at the 5-position by amines; conversion of aminoguanidine derivatives using sodium nitrite; and azide-mediated construction of the tetrazole ring. The latter category includes the addition of azide to carbodiimides and cyanamides, as well as azide substitution reactions involving chloroformamidines, aminoiminomethanesulfonic acid, and substituted benzotriazole-derived carboximidamides.

The IBX-mediated approach represents a distinct variation of the azide-based tetrazole synthesis, in which readily accessible 1,3-disubstituted thioureas serve as precursors to carbodiimide intermediates through oxidative desulfurization. Earlier methods based on this general transformation frequently employed heavy-metal-based desulfurizing agents, particularly mercury and lead salts, raising concerns regarding toxicity and environmental impact. Molecular iodine has subsequently been explored as a milder alternative and provided promising results; however, limitations in substrate scope have been reported, particularly for the synthesis of certain *N*,1-dialiphatic-1*H*-tetrazol-5-amines. The development of an IBX-based protocol therefore provides a useful complementary strategy with broader synthetic applicability.

Reaction conditions were initially optimized using 1-butyl-3-phenylthiourea (8b) as a model substrate. The effects of the amount of TEA and sodium azide, reaction time, and solvent were systematically evaluated. Among the solvents examined, including DMSO, DMF, acetonitrile, dichloromethane, and THF, DMF provided the cleanest reaction profile and the highest product yield. The optimized procedure involved treatment of the thiourea with IBX

Table 5. Substrate Scope for 5-Aminotetrazoles.



and TEA in DMF, followed by the portionwise addition of sodium azide and continued stirring at room temperature. Under these conditions, a range of 5-aminotetrazoles **9** was obtained in good to excellent yields.

The substrate-scope studies revealed several notable trends. 1-Phenyl-5-aminotetrazole was obtained in good yield from the corresponding terminal phenylthiourea. In general, *N*,1-disubstituted tetrazoles were formed in particularly good yields when at least one aromatic substituent was present in the starting thiourea. In contrast, thioureas bearing two aliphatic substituents generally afforded the corresponding products in moderate yields. These observations indicate that the electronic and steric characteristics of the substituents attached to the thiourea substantially influence the efficiency of carbodiimide formation and subsequent azide addition/cyclization.

An important mechanistic consideration arises with unsymmetrically substituted thioureas, for which the formation of regioisomeric tetrazoles is theoretically possible. The observed preference for *N*-aryl-substituted tetrazoles can be rationalized in terms of the differing basicities of the amine substituents attached to the thiourea-derived carbodiimide. Following formation of the unsymmetrical carbodiimide intermediate, protonation preferentially occurs at the more basic nitrogen site. Subsequent nucleophilic attack by azide generates a guanidyl-type intermediate (**E**), which undergoes electrocyclization to furnish the tetrazole framework.

The observed regioselectivity can therefore be correlated with the relative pK_a^* values of the precursor amines. The amine with lower basicity preferentially becomes incorporated into the tetrazole ring, whereas the more basic amine remains associated with the exocyclic amino functionality. This mechanistic rationale provides a useful explanation for the regioisomeric preference observed in the synthesis of unsymmetrical 5-aminotetrazoles.

Overall, the IBX/TEA-mediated oxidative desulfurization–azide cyclization sequence provides a concise and efficient route to structurally diverse 5-aminotetrazoles. The methodology combines the advantages of a metal-free oxidative desulfurization process with direct tetrazole-ring construction, thereby offering a valuable alternative to conventional heavy-metal-mediated approaches. The ability to generate the key carbodiimide intermediate *in situ* and subsequently trap it with an external nucleophile further highlights the versatility of IBX-mediated sulfur chemistry for the synthesis of nitrogen-rich heterocyclic architectures.

Synthesis of 3-Amino-1,2,4-triazoles

The versatility of the IBX-mediated oxidative desulfurization strategy was further demonstrated through the synthesis of 3-amino-1,2,4-triazoles from readily accessible 1,3-disubstituted thioureas. This transformation represents another example of the intermolecular trapping of an *in situ* generated carbodiimide intermediate by an external nitrogen nucleophile. In this case, formyl hydrazide serves as the nucleophilic partner, enabling subsequent cyclization to furnish the corresponding 3-amino-1,2,4-triazole derivatives.

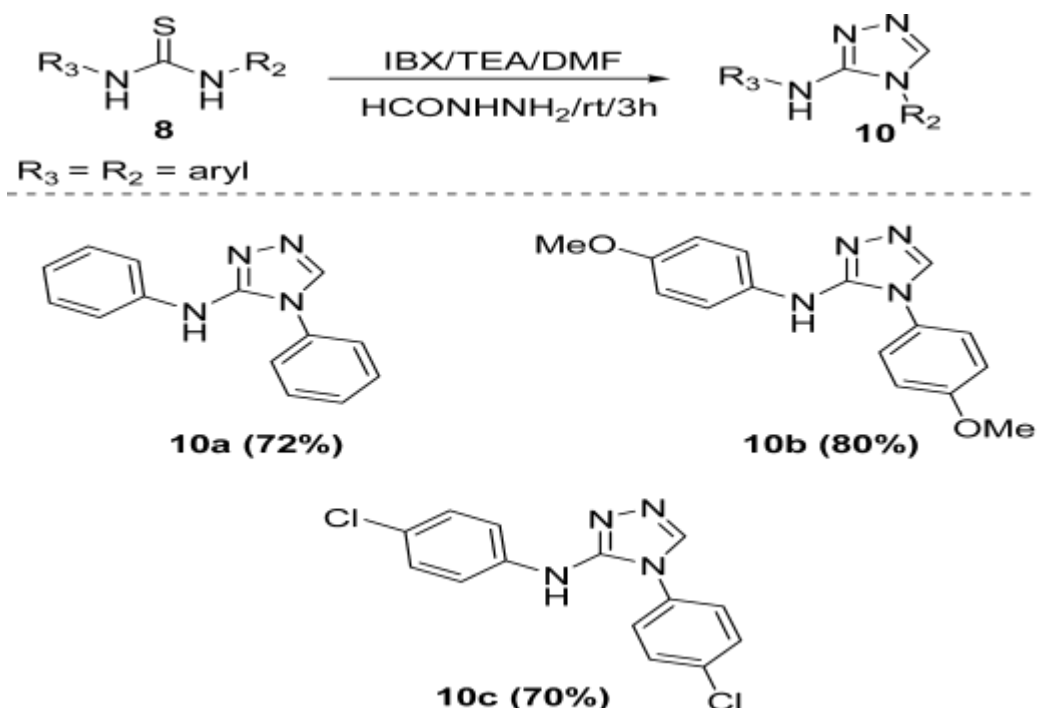
1,2,4-Triazoles constitute an important class of nitrogen-containing heterocycles with considerable significance in medicinal and pharmaceutical chemistry. Their structural and electronic characteristics contribute to a broad spectrum of biological activities, including antifungal, antimicrobial, antiviral, anti-inflammatory, antiasthmatic, and antiproliferative effects. In addition, the 1,2,4-triazole ring has been employed as an amide-bond bioisostere in medicinal chemistry, where its incorporation into molecular frameworks can influence receptor interactions, metabolic stability, and pharmacokinetic properties. Consequently, efficient approaches for the preparation of functionalized 1,2,4-triazoles continue to attract substantial synthetic interest.

Several methodologies have been developed for the synthesis of 3-amino-1,2,4-triazoles. Early approaches commonly employed mercury(II) salts for oxidative desulfurization of thiourea derivatives, while more recent procedures have investigated silver salts as alternative desulfurizing agents. Although these methods can provide the desired heterocycles, the use of heavy-metal reagents presents significant concerns associated with toxicity, waste generation,

and environmental compatibility. Other approaches based on solid-phase synthesis have employed acid-hydrazide resins, amidines, molecular sieves, and resin-bound thioamide intermediates. Such strategies may involve relatively harsh reaction conditions, multistep procedures, and prolonged reaction times, thereby limiting their practical attractiveness.

In this context, the IBX/TEA system offers a complementary metal-free oxidative strategy for the construction of 3-amino-1,2,4-triazoles. The reaction was explored using a series of 1,3-disubstituted thioureas in combination with formyl hydrazide. The results demonstrated that

Table 6. Representative Examples for 3-(Substituted Amino)-1,2,4-triazoles



the electronic nature of the substituents influences the efficiency of the transformation. Thioureas containing electron-donating substituents generally afforded the corresponding triazoles in better yields than substrates bearing electron-withdrawing substituents. Although the substrate scope reported for this transformation was relatively limited, the results established the feasibility of using IBX-mediated oxidative desulfurization and nucleophilic trapping as a route to amino-substituted 1,2,4-triazoles.

Overall Significance of IBX-Mediated Azole Synthesis

The collective studies demonstrate the multifaceted utility of the homogeneous IBX/TEA system for the one-pot construction of structurally diverse azoles through oxidative desulfurization. A central feature of this chemistry is the generation of reactive carbodiimide-like intermediates *in situ* from readily accessible sulfur-containing precursors, followed by their selective trapping with appropriate nucleophiles.

The reported transformations can broadly be categorized according to the mode of trapping of the reactive intermediate. **Intramolecular trapping** of carbodiimide intermediates generated from thiosemicarbazides and bis-diarylthioureas provides efficient access to 2-amino-1,3,4-oxadiazoles and 2,5-diamino-1,3,4-thiadiazoles, respectively. In contrast, **intermolecular trapping** of carbodiimide intermediates derived from thioamides and 1,3-disubstituted thioureas with external nucleophiles such as azide and hydrazide enables the synthesis of highly substituted tetrazoles and 1,2,4-triazoles.

An important advantage of these methodologies is their reliance on IBX as a comparatively mild, metal-free oxidant, in contrast to several earlier approaches that employed toxic heavy-metal reagents for oxidative desulfurization. The reactions generally proceed under relatively mild conditions and, in several cases, provide the desired heterocycles rapidly and in good to excellent yields. The ability to transform simple and readily available sulfur-containing substrates into structurally complex nitrogen-rich heterocycles in a one-pot fashion represents a significant synthetic advantage.

From a broader perspective, the chemistry illustrates the potential of oxidative desulfurization not merely as a functional-group transformation but as a strategic entry point to heterocycle construction. The combination of *in situ* carbodiimide generation and selective nucleophilic trapping enables rapid assembly of molecular frameworks containing oxadiazole, thiadiazole, tetrazole, and triazole motifs. Given the widespread occurrence and importance of these heterocycles in natural products, pharmaceutical compounds, agrochemicals, and functional materials, IBX-mediated oxidative desulfurization represents a promising platform for the development of efficient heterocyclic synthetic methodologies.

Overall, the reported studies establish IBX/TEA-mediated oxidative desulfurization as a versatile and conceptually attractive approach to azole synthesis. The methodology combines operational simplicity, rapid reaction profiles, broad nucleophile compatibility, and avoidance of toxic heavy-metal desulfurizing agents, thereby providing a useful foundation for further development of sustainable routes to biologically and technologically important nitrogen-containing heterocycles.

Conclusion

The studies discussed in this review highlight the remarkable versatility of *o*-iodoxybenzoic acid (IBX) as a hypervalent iodine(V) reagent for oxidative desulfurization and subsequent construction of structurally diverse azole frameworks. The distinctive reactivity of IBX toward sulfur-containing functionalities provides an efficient platform for transforming readily accessible thiosemicarbazides, thioureas, bis-diarylthioureas, and thioamides into valuable nitrogen- and sulfur-containing heterocycles.

A central feature of these transformations is the generation of reactive carbodiimide or carbodiimide-like intermediates *in situ* through oxidative desulfurization. These intermediates can undergo either intramolecular or intermolecular nucleophilic trapping, thereby enabling the rapid assembly of different azole scaffolds. Intramolecular cyclization of thiosemicarbazides and bis-diarylthioureas provides access to 2-amino-1,3,4-oxadiazoles and 2,5-diamino-1,3,4-thiadiazoles, respectively, whereas intermolecular trapping with azide and hydrazide nucleophiles enables the synthesis of 5-aminotetrazoles and 3-amino-1,2,4-triazoles. The successful application of a common oxidative platform to several classes of heterocycles demonstrates the broad synthetic potential of IBX-mediated sulfur chemistry.

An important aspect of these methodologies is the use of the IBX/triethylamine (TEA) system under relatively mild conditions. Several transformations proceed rapidly and afford the desired products in good to excellent yields, while exhibiting useful functional-group tolerance and chemoselectivity. The compatibility of sensitive functionalities, including phenolic and furan-containing substrates, further demonstrates the practical value of these reactions. Moreover, the ability to construct highly substituted heterocycles from simple sulfur-containing precursors in one-pot sequences provides significant advantages in terms of synthetic efficiency and molecular complexity generation.

The mechanistic studies also provide valuable insight into the role of sulfur–IBX interactions in these transformations. Initial activation of sulfur at the electrophilic iodine center, followed by oxidative desulfurization and formation of a reactive carbodiimide intermediate, appears to be a key element governing the observed reactivity. The subsequent trapping of this intermediate by oxygen-, sulfur-, azide-, or hydrazide-based nucleophiles determines the nature of the resulting heterocyclic framework. The proposed mechanisms therefore provide a useful conceptual basis for designing related IBX-mediated domino and cascade transformations.

From a sustainability perspective, these methodologies are particularly noteworthy because several conventional approaches to analogous azoles rely on corrosive, toxic, or heavy-metal-based reagents. The development of a metal-free IBX-mediated oxidative platform offers an attractive alternative that can reduce reliance on environmentally problematic desulfurizing agents. Nevertheless, further investigations into reagent economy, scalability, solvent selection, mechanistic understanding, and broader substrate scope would be valuable for establishing the full practical potential of these transformations.

The synthetic significance of this chemistry is reinforced by the importance of the resulting heterocyclic products. Oxadiazoles, thiadiazoles, triazoles, and tetrazoles are widely represented in biologically active molecules, pharmaceutical candidates, agrochemicals, materials, and functional molecular systems. Consequently, efficient approaches that enable rapid access to diverse and highly substituted members of these heterocyclic families are of considerable interest to both synthetic and medicinal chemists.

Overall, IBX-mediated oxidative desulfurization represents a powerful and versatile strategy for azole synthesis, in which sulfur removal is strategically coupled with cyclization and heterocycle formation. The combination of *in situ* carbodiimide generation, selective nucleophilic trapping, mild reaction conditions, rapid transformations, and avoidance of toxic heavy-metal desulfurizing reagents establishes this chemistry as a valuable contribution to modern heterocyclic synthesis. Future development of asymmetric variants, catalytic or recyclable IBX-based systems, continuous-flow applications, and late-stage functionalization strategies could further expand the scope and synthetic utility of this emerging class of oxidative desulfurization reactions.

References

1. Batey, R. A., & Powell, D. A. (2000). A general synthetic method for the formation of substituted 5-aminotetrazoles from thioureas: A strategy for diversity amplification. *Organic Letters*, 2(20), 3237–3240. <https://doi.org/10.1021/ol006465b>
2. Chaudhari, P. S., Dangate, P. S., & Akamanchi, K. G. (2010). *o*-Iodoxybenzoic acid mediated oxidative desulfurization of 1,3-disubstituted thioureas to carbodiimides. *Synlett*, 2010(20), 3065–3067. <https://doi.org/10.1055/s-0030-1259072>
3. Chaudhari, P. S., Pathare, S. P., & Akamanchi, K. G. (2012). *o*-Iodoxybenzoic acid mediated oxidative desulfurization initiated domino reactions for synthesis of azoles. *Journal of Organic Chemistry*, 77(8), 3716–3723. <https://doi.org/10.1021/jo2025509>
4. Frigerio, M., Santagostino, M., & Sputore, S. (1999). A user-friendly entry to 2-iodoxybenzoic acid (IBX). *Journal of Organic Chemistry*, 64(12), 4537–4538. <https://doi.org/10.1021/jo9824596>
5. Frigerio, M., Santagostino, M., & Sputore, S. (1995). Oxidation of alcohols with *o*-iodoxybenzoic acid (IBX) in DMSO: A new insight into an old hypervalent iodine reagent. *Journal of Organic Chemistry*, 60(22), 7272–7276.
6. Satam, V., Harad, A., Rajule, R., & Pati, H. (2010). 2-Iodoxybenzoic acid (IBX): An efficient hypervalent iodine reagent. *Tetrahedron*, 66, 7659–7706.
7. Duschek, A., & Kirsch, S. F. (2011). 2-Iodoxybenzoic acid—A simple oxidant with a dazzling array of potential applications. *Angewandte Chemie International Edition*, 50, 1524–1552.
8. Zhdankin, V. V. (2011). Organoiodine(V) reagents in organic synthesis. *Journal of Organic Chemistry*, 76(4), 1185–1197. <https://doi.org/10.1021/jo1024738>
9. Zhdankin, V. V., & Stang, P. J. (2008). Chemistry of polyvalent iodine. *Chemical Reviews*, 108(12), 5299–5358. <https://doi.org/10.1021/cr800332c>
10. Zhdankin, V. V., & Stang, P. J. (2002). Recent developments in the chemistry of polyvalent iodine compounds. *Chemical Reviews*, 102(7), 2523–2584.
11. Stang, P. J., & Zhdankin, V. V. (1996). Organic polyvalent iodine compounds. *Chemical Reviews*, 96(3), 1123–1178.
12. Yoshimura, A., & Zhdankin, V. V. (2024). Recent progress in synthetic applications of hypervalent iodine(III) reagents. *Chemical Reviews*, 124(19), 11108–11186. <https://doi.org/10.1021/acs.chemrev.4c00303>

13. Yoshimura, A., Yusubov, M. S., & Zhdankin, V. V. (2016). Synthetic applications of pseudocyclic hypervalent iodine compounds. *Organic & Biomolecular Chemistry*, 14, 4771–4781.
14. Zhdankin, V. V., Koposov, A. Y., Litvinov, D. N., Ferguson, M. J., McDonald, R., Luu, T., & Tykwinski, R. R. (2005). Esters of 2-iodoxybenzoic acid: Hypervalent iodine oxidizing reagents with a pseudobeniodoxole structure. *Journal of Organic Chemistry*, 70(16), 6484–6490. <https://doi.org/10.1021/jo051010r>
15. Dess, D. B., & Martin, J. C. (1983). Readily accessible 12-I-5-I oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *Journal of Organic Chemistry*, 48, 4155–4156. <https://doi.org/10.1021/jo00170a070>
16. Tohma, H., & Kita, Y. (2004). Hypervalent iodine reagents for the oxidation of alcohols and their application to complex molecule synthesis. *Advanced Synthesis & Catalysis*, 346, 111–124.
17. Magdziak, D., Rodriguez, A. A., Van De Water, R. W., & Pettus, T. R. R. (2002). Regioselective oxidation of phenols to *o*-quinones with *o*-iodoxybenzoic acid (IBX). *Organic Letters*, 4(2), 285–288.
18. Tohma, H., & Kita, Y. (2004). Hypervalent iodine reagents for organic synthesis. *Chemical Communications*, 2004, 1441–1450.
19. Zhdankin, V. V. (2009). Hypervalent iodine(III) reagents in organic synthesis. *ARKIVOC*, 2009, 1–62.
20. Yella, R., Khatun, N., Rout, S. K., & Patel, B. K. (2011). Tandem regioselective synthesis of tetrazoles and related heterocycles using iodine. *Organic & Biomolecular Chemistry*, 9(9), 3235–3245. <https://doi.org/10.1039/C0OB01007C>
21. Sarvary, A., & Maleki, A. (2015). A review of syntheses of 1,5-disubstituted tetrazole derivatives. *Molecular Diversity*, 19(1), 189–212. <https://doi.org/10.1007/s11030-014-9553-3>
22. Moraes, A. M., da Silva, T. L., & de Mattos, M. C. S. (2023). 5-Aminotetrazoles—An overview of synthetic methodologies through the desulfurization of thioureas. *Current Organic Chemistry*, 27(15), 1319–1328. <https://doi.org/10.2174/0113852728263929230919074722>
23. Yu, Y., Ostresh, J. M., & Houghten, R. A. (2004). Solid-phase synthesis of 5-aminotetrazoles. *Tetrahedron Letters*, 45(41), 7787–7789. <https://doi.org/10.1016/j.tetlet.2004.07.160>
24. Oliveira, C. S., Lira, B. F., Barbosa-Filho, J. M., Lorenzo, J. G. F., & Athayde-Filho, P. F. (2012). Synthetic approaches and pharmacological activity of 1,3,4-oxadiazoles: A review of the literature from 2000–2012. *Molecules*, 17(9), 10192–10231. <https://doi.org/10.3390/molecules170910192>
25. Kumar, R., Kukreti, N., & Sharma, U. (2024). Substrate-based synthetic strategies and biological activities of 1,3,4-oxadiazole: A review. *Chemical Biology & Drug Design*. <https://doi.org/10.1111/cbdd.14552>
26. Lakshman, M. K., & Kumar, A. (2017). Updates on synthesis and biological activities of 1,3,4-oxadiazole: A review. *Synthetic Communications*, 47(20), 1805–1847. <https://doi.org/10.1080/00397911.2017.1360911>
27. Matysiak, J. (2015). Biological and pharmacological activities of 1,3,4-thiadiazole based compounds. *Mini-Reviews in Medicinal Chemistry*, 15(9), 762–775. <https://doi.org/10.2174/1389557515666150519104057>
28. Obakachi, V. A., Kushwaha, B., Kushwaha, N. D., Mokoena, S., Ganai, A. M., Pathan, T. K., van Zyl, W. E., & Karpoomath, R. (2021). Synthetic and anti-cancer activity aspects of 1,3,4-thiadiazole containing bioactive molecules: A concise review. *Journal of Sulfur Chemistry*, 42(6), 670–691.
29. Aggarwal, R., & Sumran, G. (2020). An insight on medicinal attributes of 1,2,4-triazoles. *European Journal of Medicinal Chemistry*, 205, 112652. <https://doi.org/10.1016/j.ejmech.2020.112652>
30. Gupta, O., Pradhan, T., & Chawla, G. (2023). An updated review on diverse range of biological activities of 1,2,4-triazole derivatives: Insight into structure activity relationship. *Journal of Molecular Structure*, 1274, 134487. <https://doi.org/10.1016/j.molstruc.2022.134487>
31. Monakhova, N. Y., et al. (2021). Recent advances in the chemistry of 1,2,4-triazoles: Synthesis, reactivity and biological activities. *Tetrahedron Letters*, 86, 153518. <https://doi.org/10.1016/j.tetlet.2021.153518>