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Graphical Abstract

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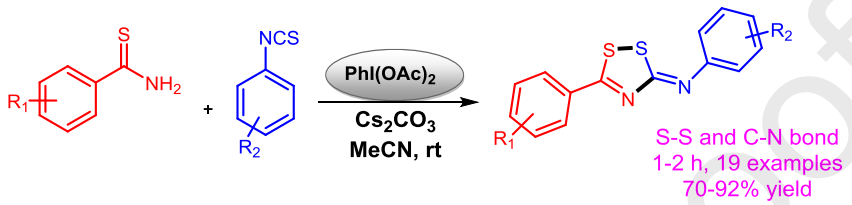

- Transition-metal-free
- Regioselectivity
- High efficiency
- Wide substrate scope
- Scalable
- Insensitive to air and moisture

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Transition-metal-free PhI(OAc)$_2$-mediated oxidative S-S and C-N bond formation: Regioselective synthesis of 3*H*-1,2,4-dithiazol-3-imines

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ABSTRACT

An effective and new approach is proposed for the synthesis of regioselective 3*H*-1,2,4-dithiazol-3-imines through S-S and C-N bond formation for the first time from benzothioamides and isothiocyanates under transition-metal-free conditions. This protocol proceeds by using hypervalent iodine(III) compound of phenyliodine diacetate (PhI(OAc)$_2$) having additive cesium carbonate in acetonitrile solution at room temperature to provide facile access to 3*H*-1,2,4-dithiazol-3-imine derivatives from readily available starting materials with broad substrate scope, insensitive to air and moisture, regioselectivity and affluent up to gram scale.

Chemistry of heterocyclic compounds is most interesting and challenging branch in organic chemistry, in which the heterocycles containing both sulphur and nitrogen atoms could furnish development of new synthetic strategies and important biological activities.[1] Among the divergent heterocyclic scaffolds, dithiazoles (both 1,2,3- and 1,2,4-) and their derivatives provided with various interesting biological activities, particularly, anti-microbial activity.[2] Some of the important derivatives of dithiazoles having antifungal and antibacterial activities are shown in Figure 1. *N*-3-(1,2,4-Dithiazole-5-thione)-β-resorcylcarbothioamide, 5,6-dihydro-3*H*-imidazo[2,l-*c*]-l,2,4-dithiazole-3-thione and *N*-arylimino-l,2,3-dithiazoles were found to exhibit antifungal activity,[3-5] whereas, 5-(4-chloro-[1,2,3]dithiazol-5-ylideneamino)-naphthalen-1-ol possesses notable antifungal as well as antibacterial activities.[6] These dithiazole compounds are reported to having various modes of action and their targets comprise enzymes such as leucine arylamidase, α-glucosidase, esterases, lipases, *N*-acetyl-β-glucosaminidase, and alkaline phosphatase.[3]

Phenyliodine(III) diacetate (PhI(OAc)$_2$) commonly known as PIDA is the most important and commercially available representative of hypervalent iodine(III) carboxylates. Recently, important bioactive molecules of hetercyclic compounds were successfully synthesized by using hypervalent iodine(III) compounds. In particularly, PhI(OAc)$_2$ has been successfully employed in the C-C, C-N, C-O, C-S and N-S bond formation reactions.[7] Hence, the construction of efficient and sustainable heterocyclic ring formations employing PhI(OAc)$_2$ is still highly desirable. Herein, we report a strategy for heteroatom-heteroatom bond formation of S-S for the first time using PhI(OAc)$_2$ successfully.

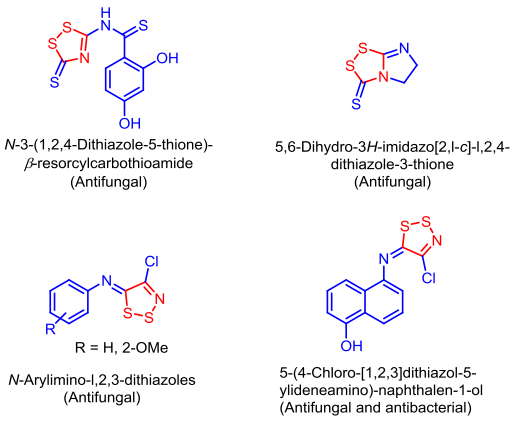
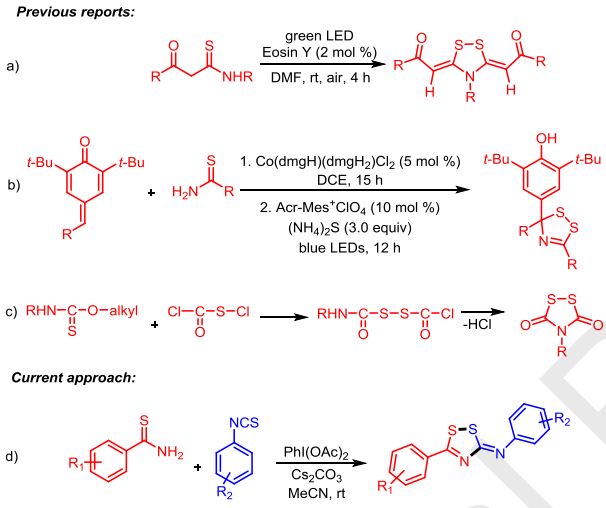


Figure 1. Selective important antifungal and antibacterial derivatives of dithiazoles.

Due to having various pharmaceutical applications[8] of 1,2,4-dithiazoles few methods were developed as shown in Scheme 1. Singh group reported an open pot strategy of dimerization/deaminative cyclization cascade process from *β*-ketothioamides using eosin Y as a photoinitiator for the synthesis of 1,2,4-dithiazolidine derivatives in presence of visible-light at ambient temperature (Scheme 1a).[9] Pan and his group developed a strategy using visible light for the synthesis of 1,2,4-dithiazoles

presence of acridinium salt (Scheme 1b).[10] Kuhle group reported a strategy for the synthesis of 1,2,4-dithiazolidine-3,5-diones from *O*-alkyl esters of *N*-monosubstituted thiocarbamic acids and chlorocarbonylsulfenylchloride (Scheme 1c).[11] However, majority of shortcomings of these protocols occurred due to the general requirement of special structural features in substrates, use of metal catalysts and harsh reaction conditions. To the best of our knowledge, there is no transformation method available for the synthesis of 1,2,4-dithiazoles using $PhI(OAc)_2$. In continuation of our previous achievements for the synthesis of biologically important heterocyclic scaffolds,[12] herein, we propose an efficient regioselective synthesis of 3*H*-1,2,4-dithiazol-3-imines employing $PhI(OAc)_2$ from readily available benzothioamides and isothiocyanates for the first time at ambient temperature (Scheme 1d). This protocol constitutes an efficient and novel access for the 3*H*-1,2,4-dithiazol-3-imine derivatives and which to far has not been reported in the literature.

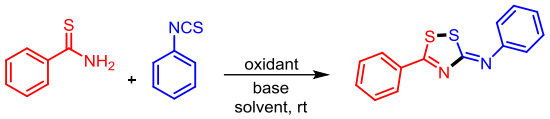
Scheme 1. Previous reports and current approach for the synthesis of 1,2,4-dithiazoles.



We started our analysis by following the reaction of benzothioamides **1a** and isothiocyanates **2a** using $PhI(OAc)_2$ as an oxidant (Table 1). As useful starting materials, thioamides behave both as nucleophiles and electrophiles and widely used in the synthesis of many heterocyclic compounds comprising thiophene, thiazole, and pyrrole.[13] When a mixture of **1a** (1.0 equiv.) and **2a** (1.0 equiv.) in $CHCl_3$ using $PhI(OAc)_2$ (1.0 equiv.) at room temperature, satisfyingly, oxidative-cyclization proceeded smoothly and affording desired product 1,2,4-dithiazole (**3a**) through S-S and C-N bond formation in only 15% yield (Table 1, entry 1). To increase the yield of the product, we have monitored with several solvents such as DMSO, MeOH, MeCN, and toluene and it was found that MeCN was worked better than other solvents (entries 2-5). Next, to improve the yield of the product screening of various bases as additive revealed Cs_2CO_3 (1 equiv.) as the base of choice (Table 1, entry 8).[14] KOH, NaOH and LiOH gave lower yields (Table 1, entries 6, 7 and 9). With these control experiments, all of the starting materials with $PhI(OAc)_2$ oxidant and base were essential for this reaction. Several other oxidants $PhI(OCOCF_3)_2$, I_2, and PhIO were screened, but only lower yields of **3a** could be observed in all the cases (Table 1, entries 10-12). Further screening the equivalence of oxidant, no affect of yield was observed when increasing the amount of $PhI(OAc)_2$ but the yield of the product significantly decreased with decreasing amount of $PhI(OAc)_2$ observed (Table 1, entries 13 and 14). Thus, the most efficient

l as follows: 1 equiv of **1a** and 1 equiv of **2a** with 1 equiv of PIDA in the presence of 1 equiv of the additive base Cs_2CO_3 in acetonitrile at room temperature (Table 1, entry 8).

Table 1. Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	Oxidant (x equiv)	Base (1 equiv)	Solvent	Yield (%)[b]
1	$PhI(OAc)_2$ (1)	-	$CHCl_3$	15
2	$PhI(OAc)_2$ (1)	-	DMSO	20
3	$PhI(OAc)_2$ (1)	-	MeOH	10
4	$PhI(OAc)_2$ (1)	-	MeCN	30
5	$PhI(OAc)_2$ (1)	-	toluene	5
6	$PhI(OAc)_2$ (1)	KOH	MeCN	70
7	$PhI(OAc)_2$ (1)	NaOH	MeCN	75
8	**$PhI(OAc)_2$ (1)**	**Cs_2CO_3**	**MeCN**	**90**
9	$PhI(OAc)_2$ (1)	LiOH	MeCN	60
10	$PhI(OCOCF_3)_2$ (1)	Cs_2CO_3	MeCN	20
11	I_2 (1)	Cs_2CO_3	MeCN	Trace
12	PhIO (1)	Cs_2CO_3	MeCN	10
13	$PhI(OAc)_2$ (1.5)	Cs_2CO_3	MeCN	90
14	$PhI(OAc)_2$ (0.5)	Cs_2CO_3	MeCN	44

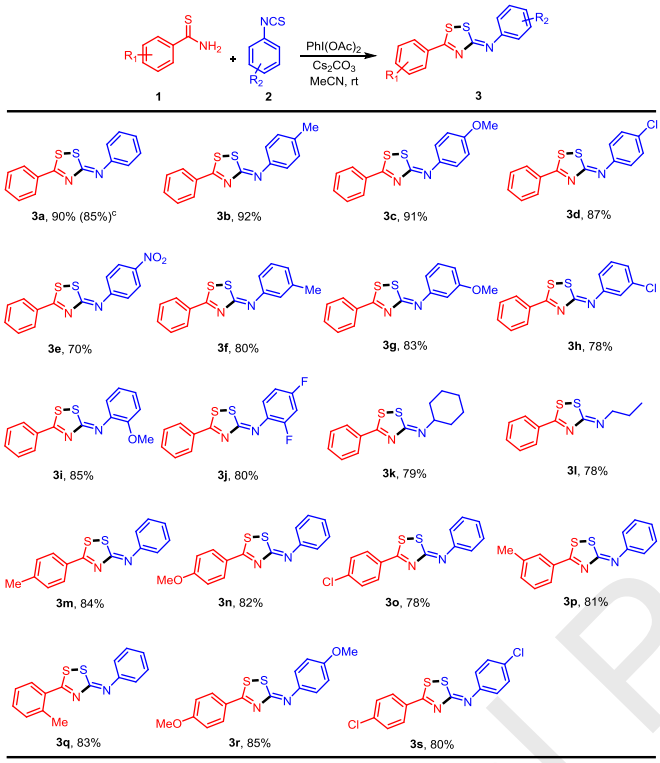
[a]Reaction conditions: **1a** (1 mmol, 1 equiv), **2a** (1 mmol, 1 equiv), catalyst (x equiv), base (1 equiv) and solvent (2 mL) at rt for 1 to 2 h.
[b]Isolated yield.

With the help of optimized reaction conditions, we explored the applicability of this regioselective oxidative cyclization strategy, and the results are summarized in Table 2. The high efficiency shown by the model reaction was efficiently translated to a wide variety of substituted 3*H*-1,2,4-dithiazol-3-imine derivatives (**3**) with different benzothioamides (**1**) and isothiocyanates (**2**) using $PhI(OAc)_2$ oxidative system provided good to excellent yields in all cases. Isothiocyanates having electron-donating groups like methyl and methoxy at *para*-, *meta*- and *ortho*-positions afforded the corresponding 3*H*-1,2,4-dithiazol-3-imines (**3b**, **3c**, **3f**, **3g** and **3i**) in high yields (80-92%). Conversely, electron-deficient halogen substituents like -Cl and -F at *para*-, *meta*- and *ortho*-positions delivered respective 3*H*-1,2,4-dithiazol-3-imines (**3d**, **3h** and **3j**) in good yields (78-87%). Moreover, strong electron-withdrawing $-NO_2$ group provides good yield of the product **3e** (70%). Interestingly, electron-deficient disubstituted fluoro phenylisothiocyanate underwent oxidative cyclization smoothly provided the dithiazole product **3j** in good isolated yield (80%). In addition, an alicyclic isothiocyanate such as cyclohexyl isothiocyanate could also be examined with the reaction conditions and furnished the corresponding product **3k** in 79% yield. It is worthy to mention that an aliphatic propyl isothiocyanate also delivered the desired product **3l** in moderate yield. Further to extend the substrate scope and limitations of the reaction, we studied effect of different substituents present at the benzothioamide ring with phenyl isothiocyanates, which proceeded proficiently to afford the corresponding 3*H*-1,2,4-dithiazol-3-imines in good to excellent yields. As shown in Table 2, benzothioamide bearing electron-donating groups such as methyl and methoxy at *para*-, *meta*- and *ortho*-positions of the phenyl ring afforded corresponding products **3m**, **3n**, **3p** and **3q** in good to excellent yields. Additionally, benzothioamide substituted with electron-withdrawing group like -Cl at *para*-position afforded the desired product in good yield (**3o**). It is notable that the reaction

succ

donating group (-OMe) presenting on the both benzothioamide and phenyl isothiocyanate substrates. Conversely, good yield of the product **3s** obtained when electron-withdrawing group (-Cl) presenting on the both substrates. Further structural confirmation of compound **3o** was unambigiously studied by X-ray diffraction analysis (Figure 2). It should be observed that the practical applicability of this oxidative cyclization strategy was confirmed successfully by the gram-scale synthesis under optimized reaction conditions (Table 2, **3a**).

Table 2. Substrate scope of the 3*H*-1,2,4-dithiazol-3-imines.[a,b]



[a]Reaction conditions: **1** (1 mmol, 1 equiv), **2** (1 mmol, 1 equiv), $PhI(OAc)_2$ (1 equiv), Cs_2CO_3 (1 equiv) and MeCN (2 mL) at rt for 1 to 2 h.
[b]Isolated yield.
[c]The reaction was conducted on gram scale.

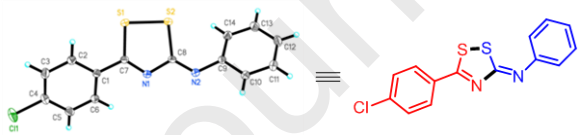
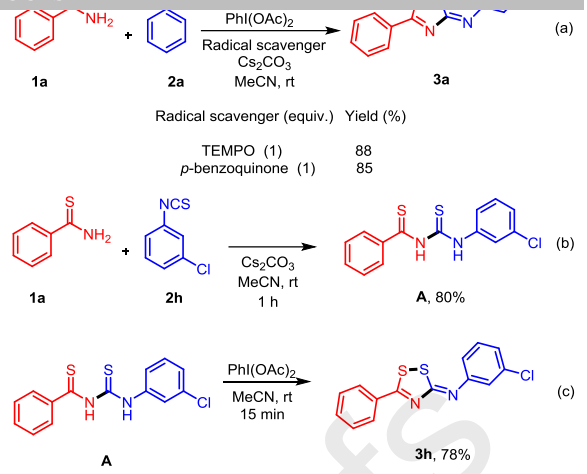


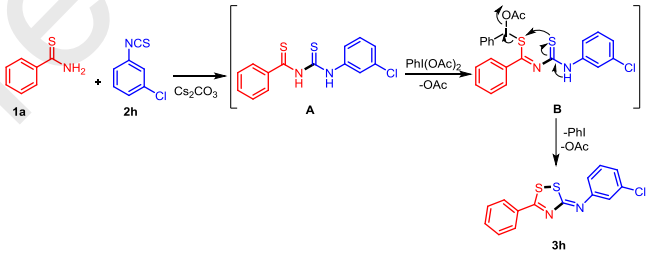
Figure 2. Crystallographic representation of compound **3o**.

Next we turned to explain the possible reaction pathway, few control experiments were performed (Scheme 2). The experiments were conducted in the presence of free radical trapping reagents like 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) and *p*-benzoquinone (BQ) under the optimized reaction conditions and no significant effect was noticed (Scheme 2a). These results summarized that an ionic mechanism was probably involved in this transformation. When the benzothioamide **1a** and 3-chloro phenyl isothiocyanate **2h** undergo reaction in the presence of Cs_2CO_3 with the absence of $PhI(OAc)_2$, the intermediate **A** (Scheme 2b) was obtained, which was confirmed by its charecteristic free NH protons obsereved in ^1H NMR data (see Supporting Information). This intermediate **A** reacts with $PhI(OAc)_2$ to give our desired product **3h** in 78% yield (Scheme 2c).



Scheme 2. Control experiments.

Based on above experimental results and previous reports,[12b,15] a possible mechanism has been proposed for the formation of **3h** as an example for this oxidative regioselective approach (Scheme 3). Initially, the benzothioamide (**1a**) reacts with 3-chloro phenyl isothiocyanate (**2h**) in presence of Cs_2CO_3 to generate the intermediate **A**. The intermediate **A** reacts with $PhI(OAc)_2$ to form the thiourea intermediate **B**, followed by intramolecular nucleophilic attack on the sulfur atom by the another sulfur atom, the removal of iodobenzene and acetic acid takes place to afford the desired product **3h**.



Scheme 3. Proposed reaction mechanism.

In summary, we have developed the first regioselective oxidative cyclization of transition-metal-free strategy for the synthesis of 3*H*-1,2,4-dithiazol-3-imines by using an efficient oxidative reagent $PhI(OAc)_2$ from benzothioamides and isothiocyanates through C-N and S-S bond formation. These compounds are the novel dithiazole heterocyclic scaffolds.

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16. For spectral data and experimental procedures, please see *Supporting Information.*

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